IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SANTARUS, INC., a Delaware corporation, and THE CURATORS OF THE UNIVERSITY OF MISSOURI, a public corporation and body politic of the State of Missouri,	)	
Plaintiffs,	)	C.A. No. 07-551-GMS
v.	)	
PAR PHARMACEUTICAL, INC., a Delaware corporation,	)	
Defendant.	)	

DEFENDANT PAR PHARMACEUTICAL, INC.'S
ANSWERING BRIEF IN OPPOSITION TO SANTARUS'S MOTION TO DISMISS

Of Counsel:
Edgar H. Haug, Esq.
Daniel G. Brown, Esq.
FROMMER LAWRENCE & HAUG LLP
745 Fifth Avenue
New York, New York 10151
(212) 588-0800

Frederick L. Cottrell, III (#2555)
Cottrell@rlf.com
Steven J. Fineman (#4025)
Fineman@rlf.com
RICHARDS, LAYTON & FINGER, P.A.
One Rodney Square
920 North King Street
Wilmington, Delaware 19801
(302) 651-7700
Attorneys for Defendant

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I. NATURE AND STAGE OF THE PROCEEDING

This is a Hatch-Waxman case involving two consolidated actions, C.A. No. 07-551 (GMS) and C.A. No. 07-827 (GMS). (07-827 D.I. 9); (D.I. 15). The two consolidated actions arose after defendant Par Pharmaceutical, Inc. ("Par") filed two Abbreviated New Drug Applications (ANDAs) with FDA seeking regulatory approval to market the generic pharmaceutical products omeprazole/sodium bicarbonate capsules (ANDA No. 78-966, "Par's capsule ANDA") and powder for oral suspension (ANDA No. 79-182, "Par's powder ANDA"). (D.I. 9, Ans. ¶ 13); (07-827 D.I. 8, Ans. ¶ 14). Plaintiff Santarus, Inc. ("Santarus") markets omeprazole/sodium bicarbonate capsules and powder products under the brand name Zegerid®. (D.I. 9, Ans. ¶ 12); (07-827 D.I. 8, Ans. ¶ 13).

Plaintiffs Santarus and The Curators of the University of Missouri (collectively, "Plaintiffs") sued Par on September 13, 2007, alleging that Par's capsule ANDA product infringed three patents listed in FDA's *Orange Book* with respect to Zegerid® capsules. (D.I. 9, Ans. ¶¶ 17, 21, 25). Par answered and counterclaimed, denying infringement and alleging that the asserted patents were invalid over the prior art and were unenforceable due to Plaintiffs' inequitable conduct during the prosecution of the patents. (D.I. 9, Ans. ¶¶ 17, 21, 25, Def. ¶ 3, Countercl. ¶¶ 25-27).

On December 20, 2007, Plaintiffs filed a second suit against Par alleging that Par's powder ANDA product infringed four patents listed in FDA's *Orange Book* with respect to Zegerid® powder. (07-827 D.I. 8, Ans. ¶¶ 19, 23, 27, and 31). Three of the asserted patents were the same patents Plaintiffs asserted in the earlier-filed suit concerning Par's capsule ANDA. *cf* (D.I. 9, Ans. ¶¶ 17, 21, 25); (07-827 D.I. 8, Ans. ¶¶ 19, 23, 27, and 31).

On January 30, 2007, Par filed its Amended Answer and Counterclaims, denying infringement and alleging that the four asserted patents were invalid over the prior art and were

unenforceable due to Plaintiffs' inequitable conduct in prosecuting the patents. (07-827 D.I. 8, Ans. ¶¶ 19, 23, 27, and 31, Def. ¶¶ 3-4, Countercl. ¶¶ 27-93). In addition, Par filed a declaratory judgment counterclaim alleging noninfringement, invalidity and unenforceability of the fifth *Orange Book* patent for Zegerid® powder (U.S. Patent No. 5,840,737, the "'737 patent"). (07-827 D.I. 8, Countercl. ¶¶ 27-93).

On February 11, 2008 this Court held a Rule 16 conference and, on March 4, 2008, entered a Scheduling Order which, *inter alia*, consolidated the two actions and set the case for trial beginning July 13, 2009. (07-827 D.I. 9); (D.I. 15). The cases are now in the fact discovery period. (07-827 D.I. 9); (D.I. 15).

On February 22, 2008, Plaintiff Santarus moved to dismiss Par's declaratory judgment counterclaims with respect to the '737 patent or, in the alternative, to stay proceedings on those counterclaims pending a recently-filed reissue application.[1] (D.I. 16, p. 1). Par submits this brief in opposition to Santarus's motion.

II. SUMMARY OF ARGUMENT

1. This Court has subject matter jurisdiction over Par's declaratory judgment counterclaim with respect to the '737 patent. Plaintiffs sued Par on four of the five patents that Plaintiffs listed in FDA's *Orange Book* with respect to the pharmaceutical product at issue in this case. The Federal Circuit has recently held that indistinguishable facts give rise to subject matter jurisdiction as a matter of law. *Teva Pharms. U.S.A., Inc. v. Novartis Pharms. Corp.*, 482 F.3d 1330 (Fed. Cir. 2007) (*en banc*). Plaintiffs' recently-filed reissue proceedings do not distinguish this case from *Teva v. Novartis* because the '737 patent continues in full force during the reissue proceedings, and Plaintiffs have not provided Par with a covenant not to sue on the '737 patent.

[1] It does not appear that Plaintiff University of Missouri has moved to dismiss Par's declaratory judgment counterclaim, or for a stay pending reissue.

2. Judicial efficiency dictates that this Court should exercise jurisdiction over Par's declaratory judgment counterclaims. All five *Orange Book* patents derive from the same original patent application, and the '737 patent is a "parent" to all other patents in the suit. Par's inequitable conduct allegations as to all five patents derive from and include events during the prosecution of the applications that led to the '737 patent. Moreover, there is substantial overlap in the subject matter of the '737 patent claims and the other four patents. Accordingly, there will be a strong overlap in fact and expert discovery, as well as evidence at trial, between Par's allegations regarding the '737 patent and those relating to the other four patents.

3. Plaintiffs' recently-filed reissue application with respect to the '737 patent does not support staying Par's counterclaims pending the outcome of the reissue proceedings. First, the '737 patent remains legally in force unless and until Plaintiffs disclaim or surrender the patent, which they have not done. Moreover, Par faces continued uncertainty as to the '737 patent's claims because (a) the reissue statute (35 U.S.C. § 252) gives continuous effect to reissue claims that issue substantially identical to the original patent claims, and (b) Plaintiffs can unilaterally terminate the reissue proceeding at any time, leaving the original patent and all of its claims in force. In addition, Par's inequitable conduct counterclaims with respect to the '737 patent cannot, as a matter of law, be cured by reissue. Therefore, the outcome of the reissue proceeding can have no impact on these counterclaims. And Plaintiffs could have filed the reissue application long ago, but instead delayed until after these litigations began. Accordingly, it would be unfair and prejudicial to Par to continue to face uncertainty as to its rights with respect to the '737 patent by staying its declaratory judgment counterclaims.

III. STATEMENT OF FACTS

Santarus holds the NDA for Zegerid® Powder for Oral Suspension. (07-827 D.I. 8, Ans. ¶ 13). Santarus caused the '737 patent, the '346 patent, and U.S. Patent Nos. 6,645,988,

6,699,885, and 6,780,882 (collectively, the "*Orange Book* patents") to be listed in the FDA's *Orange Book* for that product. (07-827 D.I. 8, Ans. ¶ 13). The University of Missouri is identified as the assignee of the *Orange Book* patents. (07-827 D.I. 8, ¶ 12).

Par filed a paragraph IV certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) for all of the *Orange Book* patents listed in FDA's *Orange Book* for Zegerid® Powder—including the '737 patent. (07-827 D.I. 8, Ans. ¶¶ 14). Par also filed a paragraph IV certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) for all of the *Orange Book* patents listed in FDA's *Orange Book* for Zegerid® Capsules in Par's capsule ANDA. (D.I. 9, Ans. ¶ 13).

Par provided Plaintiffs with notice of its paragraph IV certifications for Par's powder ANDA and Par's capsule ANDA as well as an offer of confidential access to both ANDAs. (07-827 D.I. 8, Ans. ¶ 15-16); (D.I. 9, Ans. ¶ 14). Plaintiffs filed a complaint in this Court on September 13, 2007 alleging that the products proposed in Par's capsule ANDA infringe every *Orange Book* Patent listed for Zegerid® Capsules. (D.I. 1).

Plaintiffs also filed a complaint in this Court on December 20, 2007, alleging that the products proposed in Par's powder ANDA infringe four of the five *Orange Book* patents listed for Zegerid® Powder for Oral Suspension. (07-827 D.I. 1). Plaintiffs did not assert the '737 patent against Par in their complaint. (07-827 D.I. 1).

On January 30, 2007, Par filed its Amended Answer and Counterclaims, denying infringement and alleging that the four asserted *Orange Book* patents for Zegerid® Powder for Oral Suspension were invalid over the prior art and were unenforceable due to Plaintiffs' inequitable conduct in prosecuting the patents. (07-827 D.I. 8, Ans. ¶¶ 19, 23, 27, and 31, Def. ¶¶ 3-4, Countercl. ¶¶ 27-93).

In addition, Par filed a declaratory judgment counterclaim for noninfringement, invalidity and unenforceability for the only unasserted *Orange Book* Patent for Zegerid® Powder—the '737 patent. (07-827 D.I. 8, Countercl. ¶¶ 27-93). The '737 patent was listed in the FDA's *Orange Book* when Par filed its counterclaims and continues to be listed in the *Orange Book*.

Par recently learned that on December 12, 2007, Plaintiffs requested that the Patent Office reissue the '737 patent (a copy of Plaintiffs' request for reissue is attached hereto as Exhibit A). Plaintiffs have not represented that they plan to withdraw the patent from the *Orange Book*. Although Plaintiffs have sued Par on the four other *Orange Book* patents, and Santarus continues to list the '737 patent in the FDA's *Orange Book*, Plaintiffs have not given Par a covenant not to sue Par on the '737 patent. Nor have Plaintiffs given Par a covenant not to sue Par on any claims emerging from any reissue of the '737 patent.

IV. ARGUMENT

Santarus's motion should be denied because (1) recent Federal Circuit case law establishes that courts should exercise declaratory jurisdiction under the circumstances of this case and (2) Santarus has not met the requirements for a stay pending the outcome of Plaintiffs' recently-filed reissue application.

A. This Court Has Jurisdiction over Par's Declaratory Counterclaims Against the '737 Patent

1. The Federal Circuit's Holding in *Teva v. Novartis* Mandates a Finding That There is a Justiciable Controversy in This Case

Santarus has failed to meet the requirements to dismiss Par's counterclaim for lack of subject matter jurisdiction under the standard set forth in recent cases by the Federal Circuit and this Court. *See Teva Pharms., U.S.A., Inc. v. Novartis Pharms., Corp.*, 482 F.3d 1330 (Fed. Cir. 2007); *Merck & Co. v. Apotex, Inc.*, 488 F. Supp. 2d 418 (D. Del. 2007); *Pfizer, Inc. v. Ranbaxy*

Labs., Ltd., 525 F. Supp. 2d 680 (D. Del. 2007). In *Teva v. Novartis*, the Federal Circuit conclusively resolved the specific issue of declaratory jurisdiction under the Hatch-Waxman Act when the Patentee/NDA-holder sues on fewer than all of the *Orange Book* patents:

> A justiciable declaratory judgment controversy arises for an ANDA filer when a patentee lists patents in the *Orange Book*, the ANDA applicant files its ANDA certifying the listed patents under paragraph IV, and the patentee brings an action against the submitted ANDA on one or more of the patents. **The combination of these three circumstances is dispositive in establishing an actual declaratory judgment controversy as to all the paragraph IV certified patents, whether the patentee has sued on all or only some of the paragraph IV certified patents.**

Teva, 482 F.3d at 1344.

The court explained that filing an ANDA constitutes a single act of infringement and that every patent listed in the *Orange Book* for the product contained in the ANDA is part of the same controversy. *Id.* at 1340; *see also* 35 U.S.C. § 271(e)(2) (filing an ANDA constitutes an act of infringement). The court explained that, if filing the ANDA created sufficient controversy for the NDA holder to sue, then it should also create sufficient controversy for declaratory jurisdiction over the ANDA holder's counterclaims. *Teva*, 482 F.3d at 1342.

The Federal Circuit based its reasoning, in part, on 35 U.S.C. § 271(e)(5), which provides that, when an ANDA holder files a paragraph IV certification against an *Orange Book* patent and neither the owner of the patent nor the NDA holder bring an action for infringement within 45 days of receiving notice, the courts of the United States shall have subject matter jurisdiction in any action brought by the ANDA holder "for a declaratory judgment that such patent is invalid or not infringed." *Id.*

In the present action, all of the circumstances that the Federal Circuit held to be dispositive in *Teva v. Novartis* are present:

- Santarus caused the '737 patent and four other patents to be listed in the *Orange Book* for the Zegerid® powder product;
- Par filed an ANDA that included paragraph IV certifications with respect to all five patents listed in the *Orange Book* for Zegerid® powder, including the '737 patent; and
- Santarus filed suit on four of the five listed patents, excluding only the '737 patent.

Accordingly, it is dispositively resolved that there is a justiciable case or controversy between Par and Plaintiffs concerning the '737 patent, and declaratory jurisdiction is proper under 35 U.S.C. § 271(e)(5).

This Court's decision in *Pfizer* does not provide a basis to deny subject matter jurisdiction in this case. In *Pfizer*, this Court addressed whether subject matter jurisdiction existed when the plaintiff (1) granted the ANDA filer a covenant not to sue on one of the *Orange Book* patents **and** (2) filed a reissue application based on that patent. The defendant in the *Pfizer* case conceded that "[t]he covenant not to sue preclude[ed] infringement liability on the existing '995 patent. . . ." 525 F. Supp. 2d at 685. The circumstances in the present action are clearly distinguishable from those in the *Pfizer* case, because, among other things, Plaintiffs have not given Par a covenant not to sue on the existing '737 patent's claims, and Par remains faced with a threat of suit on the existing claims of the '737 patent.

2. Plaintiffs Have Not Given Par a Covenant Not to Sue in This Case

In this case, Plaintiffs have not given Par a covenant not to sue Par on the '737 patent. Plaintiffs acknowledge that their failure to provide a covenant not to sue distinguishes *Pfizer* from the instant case. (D.I. 16, Motion at p. 6, n. 3).

Other district courts have recognized that, in the situation where an NDA holder has failed to sue on an *Orange Book* patent, "the only circumstance in which a case or controversy might not exist would arise in the rare circumstance in which the patent owner and brand drug company have given the generic applicant a covenant not to sue, or otherwise formally acknowledge that the generic applicant's drug does not infringe." *Janssen Pharmaceutica, N.V. v. Apotex, Inc.*, Civil Action No. 06-cv-1020, 2007 WL 3014702, at *3 (D. N.J. Oct. 11, 2007); *cf Merck*, 488 F. Supp. 2d at 424.

3. Par Remains Faced with the Threat of Future Litigation Based on the '737 Patent

Santarus's brief conflates jurisdiction over the '737 patent's claims with jurisdiction over potential new claims in a future reissue patent based on the existing '737 patent. The '737 patent remains in force unless and until the patentees disclaim it or surrender it in reissue—an event that has not occurred. The reissue proceedings may also terminate at any time, leaving the patent "in effect" with its original claims. *See* Manual of Patent Examining Procedure ("MPEP") § 1416; *In re Clement*, 131 F.3d 1464, 1472 (Fed. Cir. 1997) ("Because ... the surrender of the ... patent does not take effect until the reissue patent issues, '[the] original claims ... continue to exist with their normal presumption of validity.'").

Further, any claims of the '737 patent that issue from the reissue proceedings in a form substantially identical to claims of the '737 patent are, by statute, given continuous legal effect:

> The surrender of the original patent shall take effect upon the issue of the reissued patent, ... but insofar as the claims of the original and reissued patents are substantially identical, **such surrender shall not affect any action then pending nor abate any cause of action then existing**, and the reissued patent, to the extent that its claims are substantially identical with the original patent, shall constitute a continuation thereof and have effect continuously from the date of the original patent.

35 U.S.C. § 252 (emphasis added).

Indeed, the above portion of the reissue statute makes clear that the pendency of a reissue application **does not** remove subject matter jurisdiction as to the original patent, as it clearly contemplates an action "pending" under the original patent when the reissue patent grants. *See* 35 U.S.C. § 252. Accordingly, the pendency of the reissue application does not remove the threat of suit, and does not distinguish this case from *Teva v. Novartis*. 482 F.3d at 1344.

B. This Court Should Exercise Its Discretion to Hear Par's Counterclaims Against the '737 Patent in the Interests of Justice and Judicial Economy

This Court should hear Par's counterclaims against the '737 patent because Congress intended for the ANDA holder to be certain of whether its products infringe or do not infringe the *Orange Book* patents before it launches its product. Dismissing Par's counterclaims would allow Plaintiffs to remove the '737 patent from suit, enjoy the 30-month stay on Par's ANDA approval based on the remaining *Orange Book* patents, and still bring a suit for infringement of the '737 patent's claims later. Furthermore, this Court should exercise its discretion to hear Par's counterclaims against the '737 patent in the interests of justice and judicial economy.

1. Congress Intends for Issues Involving All *Orange Book* Patents to Be Resolved Quickly and in One Proceeding

The Federal Circuit explained that the legislative history behind 35 U.S.C. § 271(e)(5) makes clear Congress's intent that an ANDA holder should be able to resolve any controversy surrounding every *Orange Book* patent covering its proposed products through a declaratory judgment in one action. *Teva*, 482 F.3d at 1342.

Plaintiffs receive the benefit of staying Par's ANDA approval process for 30 months while this lawsuit is in progress. This stay benefits Plaintiffs by keeping a competing product off the market, allowing Plaintiffs to charge a higher price for their drug products. In exchange for

the 30-month stay, Congress intended for Par to have certainty—in the form of a declaratory judgment—that Par will not be liable for patent infringement after Par brings its products to market. *See Teva*, 482 F.3d at 1342 ("The [ANDA] declaratory judgment provisions ... simply level the playing field by making it clear that the generic applicant can also seek a prompt resolution of these patent issues by bringing a declaratory judgment action if [it is not sued] ... within 45 days.") (quoting 149 Cong. Rec. S15885 (Nov. 25, 2003) (remarks of Sen. Kennedy, ranking member of the Senate HELP committee)). If Par brings its products to market without a declaratory judgment covering all *Orange Book* patents, it could face uncertainty as to its liability for damages at a later time.

Plaintiffs seek to remove the '737 patent from this case but have not provided Par with a covenant not to sue on the '737 patent or on any substantially identical reissue claims, and have not made any representations to Par that they will not sue on this patent. Removing the patent from this suit prejudices Par, unfairly benefits Plaintiffs, and gives Plaintiffs an unfair tactical advantage, contrary to Congressional intent.

2. Hearing Par's Counterclaims Would Simplify the Issues and Conserve Judicial Resources

The central issues in this case will be the noninfringement, invalidity, and unenforceability of the *Orange Book* patents. Deciding the unenforceabilty of all the *Orange Book* patents now will simplify the issues for this Court and conserve judicial resources. During its case, Par will prove that Plaintiffs committed inequitable conduct during prosecution of the '737 patent, and that the inequitable conduct infects and renders every *Orange Book* patent unenforceable.

Par has pled a strong case of inequitable conduct that includes and encompasses the events surrounding the prosecution of the '737 patent. (07-827 D.I. 8, Countercl. ¶¶ 27-93).

During prosecution of the '737 patent, Plaintiffs withheld information showing that the single named inventor of every *Orange Book* patent, Dr. Jeffrey Owen Phillips, had made numerous public disclosures of his alleged invention more than one year before the patent application was filed. (07-827 D.I. 8, Countercl. ¶¶ 36-56 and ¶¶ 57-64). For example, Dr. Phillips gave a presentation on the claimed subject matter of the *Orange Book* patents at the Society for Critical Care Medicine's annual meeting more than one year before the applicant's earliest-filed priority application. (07-827 D.I. 8, Countercl. ¶¶ 36-40, 44). The Society for Critical Care Medicine is "the largest multiprofessional organization dedicated to ... the practice of critical care," and is composed of "14,000 members in 80 countries. . . ."[2] When the applicants finally disclosed this presentation over three years later, during prosecution of the '346 patent (another *Orange Book* patent), Plaintiffs did not give any explanation as to why it was not previously disclosed and did not allege that anyone at the Society for Critical Care Medicine or anyone attending the Society for Critical Care Medicine's annual meeting owed any duty of confidentiality to applicants. (07-827 D.I. 8, Countercl. ¶ 41). The facts and discovery surrounding these events will be relevant to all of the *Orange Book* patents and therefore dismissing the '737 patent will not contribute to judicial economy.

Reissue will not cure the unenforceability of the '737 patent. *See* 35 U.S.C. § 251 (allowing for reissue on a patent that is invalid "without any deceptive intention"). Inequitable conduct in the original patent renders any reissue patent unenforceable. *Hoffman-La Roche, Inc. v. Lemmon Co.*, 906 F.2d 684, 688-89 (Fed. Cir. 1990). Further, since these issues will not be addressed by the Patent Office, the reissue proceedings will not assist this Court in resolving the issue.

[2] http://www.sccm.org/Pages/default.aspx.

This inequitable conduct during prosecution of the '737 patent also infects and renders unenforceable the other *Orange Book* patents. (07-827 D.I. 8, Countercl. ¶ 65-93). All of the remaining *Orange Book* patents are progeny of the '737 patent, and all claim similar, interrelated subject matter. All contain a terminal disclaimer over at least one other *Orange Book* patent. *Id.* Plaintiffs' motion to dismiss appears to be an attempt to lessen the impact of that inequitable conduct applicants committed during prosecution of the '737 patent will have on its other *Orange Book* patents.

Exercising jurisdiction over the '737 patent will simplify the unenforceability issue and will conserve judicial resources. If this Court retains jurisdiction over the '737 patent and determines that the *Orange Book* patents are unenforceable, this Court will not have to wait for a later suit over the '737 patent to declare it unenforceable as well.

3. The Claims of the '737 Patent Substantially Overlap with the Claims of the Other *Orange Book* Patents

The claims of the '737 patent and the other *Orange Book* patents are similar. The claims of all of the *Orange Book* patents are generally directed to a combination product of a pharmaceutical active ingredient known as a proton pump inhibitor (*e.g.*, omeprazole) and a compound to reduce stomach acidity (a buffer). Because the claims are similar, the discovery, factual findings, and arguments of the parties will also be similar and hearing Par's claims against the '737 patent in this case will simplify the issues. Also, many of the same claim terms appear throughout the patent family. Proceeding with the case on the '737 patent now will avoid inconsistent and/or duplicative claim constructions within the *Orange Book* patent family.

Furthermore, Par will need to take discovery regarding the '737 patent and its prosecution, and that discovery will be relevant to the other *Orange Book* patents. This discovery will allow Par to establish facts relevant to all of the *Orange Book* patents. While

proving that the claims of the *Orange Book* patents are anticipated and/or obvious, for example, Par will establish the scope and content of the prior art, the level of ordinary skill in the prior art, and the difference between the prior art and the claims at issue. These key factual inquiries apply to the '737 patent and the other *Orange Book* patents. If this Court denies jurisdiction over the '737 patent, Par may have to take additional discovery concerning that patent in a later suit, which will waste judicial resources as well as all parties' time and money.

Because the '737 patent plays a role in Par's invalidity and unenforceability theories, this Court should exercise its discretion to hear Par's counterclaims on the invalidity and unenforceability of the '737 patent in the interests of justice. Because the other *Orange Book* patents are similar to the '737 patent, and many of the same facts will be used to prove Par's case against all of the patents, this Court should retain jurisdiction over the '737 patent in the interests of judicial economy.

C. This Court Should Not Stay These Proceedings Pending Reissue of the '737 Patent.

This Court has discretion to grant or deny a stay. *Cognex Corp.*, No. Civ.A. 00-442-JJF, 2001 WL 34368283, at *1 (D. Del. June 29, 2001). "Courts typically cite three factors that should guide the exercise of a court's discretion when deciding whether a stay is appropriate: 1) whether the granting of a stay would cause the non-moving party to suffer undue prejudice from any delay or allow the moving party to gain a clear tactical advantage over the non-moving party; 2) whether a stay will simplify the issues for trial; and 3) whether discovery is complete and a trial date set. . . . In balancing these factors, courts must be particularly mindful of the consequences of the stay on other parties." *Id. See also St. Clair Intellectual Prop. Consultants v. Sony Corp.*, No. Civ.A. 01-557JJF, 2003 WL 25283239, at *1 (D. Del. Jan. 30, 2003).

1. A Stay Would Unduly Prejudice Par and Would Present a Clear Tactical Disadvantage to Par

As discussed above, the '737 patent remains in force, and any substantially identical claims that emerge from reissue are given continuous legal effect by the reissue statute. 35 U.S.C. § 252. Causes of action arising from those claims are also given continuous legal effect from the date of the original patent. *Id.* Filing a reissue by itself does not terminate any of Plaintiffs' rights under the '737 patent, and those proceedings could terminate at any time. Congress granted the ANDA holder the right to patent certainty so that the ANDA holder could bring its product to market quickly and benefit the public by reducing drug cost. Par should be able to adjudicate the noninfringement, invalidity, and unenforceability of every *Orange Book* patent in one suit in order to bring its products to market quickly without the delay of a stay pending reissue of the '737 patent, as Congress intended.

Granting a stay would give Plaintiffs the option of either (a) withdrawing its patent from the reissue proceedings after these proceedings end and then suing Par when it brings its product to market, or (b) if the reissue proceedings appear to be favorable to them, allow grant of the reissued patent and sue Par on the reissued '737 patent after it launches its products. Both of these situations are prejudicial to Par because Par will have to decide between launching without a court decision or foregoing making its products. At the same time, Plaintiffs sacrifice nothing because they will enjoy the 30-month stay on Par's ANDA while retaining the option of suing Par after launch. As the Federal Circuit has recognized, this is not what Congress intended when it passed the Hatch-Waxman Act.

2. Granting a Stay Will Complicate the Issues in Question and Complicate Trial of the Case

This Court will have to decide whether the '737 patent is unenforceable due to inequitable conduct because Par has alleged that the inequitable conduct committed during

prosecution of the '737 patent renders all of the *Orange Book* patents unenforceable. If this Court holds the '737 patent unenforceable for inequitable conduct and holds the other *Orange Book* patents unenforceable for infectious unenforceability, then there will not be any need for the reissue proceedings. Denying the stay allows this Court to declare the '737 patent unenforceable at the same time as the rest of the *Orange Book* patents, giving Par patent certainty and resolving all the issues in the case. And because reissue cannot cure inequitable conduct, denying the stay request will allow this Court to conclusively decide the unenforceability issue, regardless of the outcome of the reissue proceeding.

On the other hand, if this Court grants the stay, it may have to decide the issue of unenforceability of the '737 patent again later if Plaintiffs choose to bring another lawsuit against Par on the reissued patent or if the reissue proceedings terminate without the issuance of new claims.

3. A Stay Pending Reissue Will Not Assist This Court

Any reissued claims will likely be very similar to the original claims of the '737 patent. Applicants have amended claim 1 from:

> 1. A method for treating gastric acid disorders by administering to a patient a single dose of a pharmaceutical composition of omeprazole or lansoprazole in a pharmaceutically acceptable carrier consisting essentially of a bicarbonate salt of a Group IA metal wherein said administering step consists of providing to the patient orally a single dose of an aqueous solution or, suspension of the pharmaceutical composition without requiring further administration of the bicarbonate salt of the Group IA metal.

to:

> 1. A method for treating gastric acid disorders by administering to a patient a single dose of a pharmaceutical composition of omeprazole or lansoprazole <u>powder</u> in a pharmaceutically acceptable carrier consisting essentially of a bicarbonate salt of a Group IA metal wherein said administering step consists of providing to the patient orally a single dose of an aqueous solution

> or[,] suspension of the pharmaceutical composition without requiring further administration of the bicarbonate salt of the Group IA metal.

Exhibit A, Reissue Application Preliminary Amendment, at p. 2.

The addition of the word "powder" and the deletion of the comma will not assist this Court in deciding the invalidity of the '737 patent. This Court should deny the motion to stay pending reissue.

4. Plaintiffs Could Have Requested Reissue or Reexamination Earlier

Where, as here, Plaintiffs attempt to stay the case to delay or to gain a tactical advantage, district courts are reluctant to grant stays. *See, e.g. Freeman v. Minnesota Mining and Man. Co.*, 661 F. Supp. 886, 888 (D. Del. 1987). Evidence that the party is seeking to delay or to gain an advantage comes when the party was aware of the defect in the patent, but chose not to pursue reissue or reexamination at an earlier time. *See Cognex Corp.*, No. Civ.A. 00-442-JJ, 2001 WL 34368283, at *3 (reexamination).

Plaintiffs had the materials necessary to request reissue for years between the time the NDAs were approved and the time Plaintiffs received Par's notices of its paragraph IV certifications. Plaintiffs point to no recently discovered prior art or other information in their reissue application. The FDA approved the NDA for the powder products on June 15, 2004 and the *Orange Book* lists the '737 patent as covering those products. Plaintiffs were required to assess commercial embodiments of its products and make declarations under oath that its patents covered its commercial products at that time. If Plaintiffs wanted the benefit of the reissue proceeding, Plaintiffs should have requested reissue years ago, when the proceeding would not have prejudiced Par.

In fact, Plaintiffs requested reexamination of another *Orange Book* patent, U.S Patent No. 6,699,885, on August 22, 2005, more than two years before it requested reissue of the '737 patent on December 12, 2007. (D.I. 1, Comp. ¶ 8). Apparently, Plaintiffs evaluated the *Orange Book* patents' claim scope in 2005 and decided not to pursue the reissue proceeding at that time. The information regarding Plaintiffs' public uses of the alleged invention appear in submissions to the Patent Office in related patent applications in December of 2001, and cannot justify Plaintiffs' last-minute reissue filing. The current motion for a stay is a dilatory tactic, and should be denied.

Moreover, this Court has set a trial date for this case for July 13, 2009 and has previously held that a party must demonstrate "a clear case of hardship or inequity" if a proposed stay would "forestall the trial date agreed upon by the parties." *Cognex Corp.*, No. Civ.A. 00-442-JJ, 2001 WL 34368283, at *1; *see also* (D.I. 15) (setting trial date for July 13, 2009). The reissue proceeding is unlikely to conclude before the trial date set by this Court. *See E.I. Du Pont De Nemours & Co. v. Phillips Petroleum Co.*, 720 F. Supp. 373, 374 (D. Del. 1989) (reissue was requested one year before suit was filed and was pending for two years during the trial). Given Plaintiffs' delay and the stage of these proceedings, a stay at this point is inappropriate and prejudicial to Par.

V. CONCLUSION

The issues of invalidity, unenforceability, and noninfringement are central to this lawsuit. The '737 patent's claims are similar to the claims of the other *Orange Book* patents and these central issues are therefore overlapping and intertwined. This Court should hear Par's counterclaims against the '737 patent to simplify the issues and conserve judicial resources. Plaintiffs seek to stall these proceedings and to delay Par's launch of its proposed omeprazole

and sodium bicarbonate products. Congress has granted declaratory jurisdiction over Par's counterclaims to this Court by statute. Therefore, Plaintiffs' motion to dismiss for lack of subject matter jurisdiction or in the alternative to stay these proceedings pending reissue of the '737 patent should be denied.

Frederick L. Cottrell, III (#2555)
Cottrell@rlf.com
Steven J. Fineman (#4025)
Fineman@rlf.com
RICHARDS, LAYTON & FINGER, P.A.
One Rodney Square
920 North King Street
Wilmington, Delaware 19801
(302) 651-7700
Attorneys for Defendant

Of Counsel:
Edgar H. Haug, Esq.
Daniel G. Brown, Esq.
FROMMER LAWRENCE & HAUG LLP
745 Fifth Avenue
New York, New York 10151
(212) 588-0800

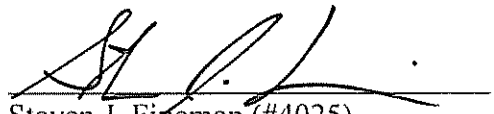
Dated: March 7, 2008

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I hereby certify that on March 7, 2008, I electronically filed the foregoing document with the Clerk of Court using CM/ECF which will send notification of such filing(s) and Hand Delivered to the following:

Jack B. Blumenfeld, Esquire
Rodger D. Smith II, Esquire
Morris, Nichols, Arsht & Tunnell LLP
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899-1347



Steven J. Fineman (#4025)
Richards, Layton & Finger, P.A.
One Rodney Square
P.O. Box 551
Wilmington, Delaware 19899
(302) 651-7700
fineman@rlf.com

EXHIBIT A

Electronic Acknowledgement Receipt

EFS ID:	2620316
Application Number:	11960934
International Application Number:	
Confirmation Number:	5332
Title of Invention:	Omeprazole Solution and Method for Using Same
First Named Inventor/Applicant Name:	Jeffrey O Phillips
Customer Number:	26565
Filer:	Joseph A. Mahoney/Andrea Hutchison
Filer Authorized By:	Joseph A. Mahoney
Attorney Docket Number:	01723512
Receipt Date:	20-DEC-2007
Filing Date:	
Time Stamp:	11:55:42
Application Type:	Reissue (Utility)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2060
RAM confirmation Number	7975
Deposit Account	130019
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)

1		Filings.PDF	660336 ba9ae3811976737bc366fc1cf42d4728 2aa163fe	yes	12

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Transmittal Reissue Application	1	1
Fee Worksheet (PTO-06)	2	3
Reissue dec filed in accordance with MPEP 1414.	4	5
Consent of Assignee accompanying the declaration.	6	7
Preliminary Amendment	8	12

Warnings:

Information:

2	Specification	US5840737.pdf	1450331 2047b2b193bd1f117b5bf88fb3aae7881 4ce3854	no	16

Warnings:

Information:

3	Fee Worksheet (PTO-06)	fee-info.pdf	8561 8717ab4f276474248b56a750f4eef9c15 f6e8c23	no	2

Warnings:

Information:

Total Files Size (in bytes):	2119228

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/50 (09-07)
Approved for use through 08/31/2010. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REISSUE PATENT APPLICATION TRANSMITTAL

Address to:

Mail Stop Reissue
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Attorney Docket No.	01723512
First Named Inventor	Phillips, Jeffrey O.
Original Patent Number	5,840,737
Original Patent Issue Date (Month/Day/Year)	11/24/1998
Express Mail Label No.	

APPLICATION FOR REISSUE OF: *(Check applicable box)* [X] Utility Patent [ ] Design Patent [ ] Plant Patent

APPLICATION ELEMENTS (37 CFR 1.173)

1. [X] Fee Transmittal Form (PTO/SB/56) (Submit a duplicate copy)
2. [ ] Applicant claims small entity status. See 37 CFR 1.27.
3. [X] Specification and Claims in double column copy of patent format *(amended, if appropriate)*
4. [X] Drawing(s) *(proposed amendments, if appropriate)*
5. [X] Reissue Oath/Declaration (original or copy) (37 C.F.R. 1.175) (PTO/SB/51 or 52)
6. [X] Power of Attorney
7. [X] Original U.S. Patent currently assigned? [X] Yes [ ] No *(If Yes, check applicable box(es))*
   - [X] Written Consent of all Assignees (PTO/SB/53)
   - [X] 37 CFR 3.73(b) Statement (PTO/SB/96)
8. [ ] CD-ROM or CD-R in duplicate, Computer Program (Appendix) or large table
   - [ ] Landscape Table on CD
9. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, items a. – c. are required))*
   - a. [ ] Computer Readable Form (CRF)
   - b. Specification Sequence Listing on:
     - i [ ] CD-ROM (2 copies) or CD-R (2 copies); **or**
     - ii [ ] paper
   - c. [ ] Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

10. [X] Statement of status and support for all changes to the claims. See 37 CFR 1.173(c).
11. [ ] Foreign Priority Claim (35 U.S.C. 119) *(if applicable)*
12. [ ] Information Disclosure Statement (IDS) PTO/SB/08 or PTO-1449
    - [ ] Copies of citations attached
13. [ ] English Translation of Reissue Oath/Declaration *(if applicable)*
14. [X] Preliminary Amendment
15. [ ] Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
16. [X] Other: Certificate of Correction

17. CORRESPONDENCE ADDRESS

[X] The address associated with *Customer Number:* 26565 ***OR*** [ ] *Correspondence address below*

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	Joseph A. Mahoney	Date	12/20/07
Name (Print/Type)	Joseph A. Mahoney	Registration No. (Attorney/Agent)	38,956

This collection of information is required by 37 CFR 1.173. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop Reissue, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/56 (10-07)
Approved for use through 08/31/2010. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REISSUE APPLICATION FEE TRANSMITTAL FORM

Docket Number (Optional)
01723512

Application as Filed – Part 1

	(1) Claims in Patent	(2) Claims Filed in Reissue Application	(3) Number Extra	Small Entity Rate ($)	Small Entity Fee ($)		Other than a Small Entity Rate ($)	Other than a Small Entity Fee ($)
Total Claims (37 CFR 1.16(i))	(A) 12	(B) 24	**** 4 =	x =			x 50 =	200
Independent Claims (37 CFR 1.16(h))	(C) 10/79	(D) 573 884-	* 2 =	x =			x 210 =	420
Application Size Fee (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).							
						or		
			Filing Fee (37 CFR 1.16(e))					310
			Search Fee (37 CFR 1.16(n))					510
			Examination Fee (37 CFR 1.16(r))					620
			Total Filing Fee					2060

Application as Amended – Part 2

	(1) Claims Remaining After Amendment		(2) Highest Number Previously Paid For	(3) Extra Claims Present	Small Entity Rate ($)	Small Entity Fee ($)		Other than a Small Entity Rate ($)	Other than a Small Entity Fee ($)
Total Claims (37 CFR 1.16(i))	*** 24	MINUS	** 20	= 4	X =			x 50 =	200
Independent Claims (37 CFR 1.16(h))	*** 573 884-	MINUS	***** 3	= 2	x =		or	x 210 =	420
Application Size Fee (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).								
				Total Additional Fee					620

* If (D) is less than (C), enter "0" in column 3. For reissues filed on or after Dec. 8, 2004, enter (D) minus 3 or "0" if (D) is less than 3.
** If the "Highest Number of Total Claims Previously Paid For" is less than 20, enter "20" in this space.
*** After any cancellation of claims.
**** If (A) is greater than 20, enter (B) - (A); if (A) is 20 or less, enter (B) - 20. For reissues filed on or after Dec. 8, 2004, enter (B) - 20.
***** For amendments filed on or after Dec. 8, 2004, enter the "Highest Number of Independent Claims Previously Paid For."
For amendments filed prior to Dec. 8, 2004, enter the higher of the Number Previously Paid or Number of Independent Claims in Patent.

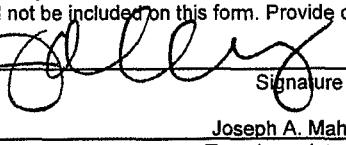
☐ Applicant claims small entity status. See 37 CFR 1.27.

☒ Please charge Deposit Account No. 13-0019 in the amount of $2,060.
A duplicate copy of this sheet is enclosed.

☒ The Director is hereby authorized to charge any additional fees under 37 CFR 1.16 or 1.17 which may be required, or credit any overpayment to Deposit Account No. 13-0019. A duplicate copy of this sheet is enclosed.

☐ A check in the amount of $ _____ to cover the filing/additional fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.



Signature — December 20, 2007 (Date)

Joseph A. Mahoney (Typed or printed name) — 38,956 (Registration Number, if applicable)

312-701-8979 (Telephone Number)

PTO/SB/56 (10-07)
Approved for use through 08/31/2010. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REISSUE APPLICATION FEE TRANSMITTAL FORM

Docket Number (Optional)
01723512

Application as Filed – Part 1

	(1) Claims in Patent	(2) Claims Filed in Reissue Application	(3) Number Extra	Small Entity Rate ($)	Small Entity Fee ($)		Other than a Small Entity Rate ($)	Other than a Small Entity Fee ($)
Total Claims (37 CFR 1.16(i))	(A) 12	(B) 24	**** 4 =	x =			x 50 =	200
Independent Claims (37 CFR 1.16(h))	(C) 10/79	(D) 573 884-	* 2 =	x =			x 210 =	420
Application Size Fee (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).							
			Filing Fee (37 CFR 1.16(e))					310
			Search Fee (37 CFR 1.16(n))					510
			Examination Fee (37 CFR 1.16(r))					620
			Total Filing Fee					2060

Application as Amended – Part 2

	(1) Claims Remaining After Amendment		(2) Highest Number Previously Paid For	(3) Extra Claims Present	Small Entity Rate ($)	Small Entity Fee ($)		Other than a Small Entity Rate ($)	Other than a Small Entity Fee ($)
Total Claims (37 CFR 1.16(i))	*** 24	MINUS	** 20	= 4	X =			x 50 =	200
Independent Claims (37 CFR 1.16(h))	*** 573 884-	MINUS	***** 3	= 2	x =			x 210 =	420
Application Size Fee (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).								
				Total Additional Fee					620

* If (D) is less than (C), enter "0" in column 3. For reissues filed on or after Dec. 8, 2004, enter (D) minus 3 or "0" if (D) is less than 3.
** If the "Highest Number of Total Claims Previously Paid For" is less than 20, enter "20" in this space.
*** After any cancellation of claims.
**** If (A) is greater than 20, enter (B) - (A); if (A) is 20 or less, enter (B) - 20. For reissues filed on or after Dec. 8, 2004, enter (B) - 20.
***** For amendments filed on or after Dec. 8, 2004, enter the "Highest Number of Independent Claims Previously Paid For."
For amendments filed prior to Dec. 8, 2004, enter the higher of the Number Previously Paid or Number of Independent Claims in Patent.

☐ Applicant claims small entity status. See 37 CFR 1.27.

☒ Please charge Deposit Account No. 13-0019 in the amount of $2,060.
A duplicate copy of this sheet is enclosed.

☒ The Director is hereby authorized to charge any additional fees under 37 CFR 1.16 or 1.17 which may be required, or credit any overpayment to Deposit Account No. 13-0019. A duplicate copy of this sheet is enclosed.

☐ A check in the amount of $ _____ to cover the filing/additional fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

Signature — December 20, 2007 (Date)

Joseph A. Mahoney (Typed or printed name) — 38,956 (Registration Number, if applicable)

312-701-8979 (Telephone Number)

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO SB-52 (09-07)
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REISSUE APPLICATION DECLARATION BY THE ASSIGNEE	Docket Number (optional) 01723512

I hereby declare that:

The residence, mailing address and citizenship of the inventors are stated below.

I am authorized to act on behalf of the following assignee: The Curators of the University of Missouri

and the title of my position with said assignee is: Vice President of Research and Economic Development

The entire title to the patent identified below is vested in said assignee.

Inventor Jeffrey O. Phillips	Citizenship U.S.A.
Residence/Mailing Address 1250 E. Nashville Church Rd. ; Ashland, MO 65010	
Inventor	Citizenship
Residence/Mailing Address	

☐ Additional Inventors are named on separately numbered sheets attached hereto.

Patent Number 5,840,737	Date of Patent Issued 11/24/1998

I believe said inventor(s) to be the original and first inventor(s) of the subject matter which is described and claimed in said patent, for which a reissue patent is sought on the invention entitled:

Omeprazole Solution and Method for Using Same

the specification of which

☒ is attached hereto.

☐ was filed on _____ as reissue application number _____ / _____

and was amended on _____
(If applicable)

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

☐ I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b). Attached is form PTO/SB/02B (or equivalent) listing the foreign applications.

I verily believe the original patent to be wholly or partly inoperative or invalid, for the reasons described below. (Check all boxes that apply.)

☐ by reason of a defective specification or drawing.

☒ by reason of the patentee claiming more or less than he had the right to claim in the patent.

☒ by reason of other errors.

REISSUE APPLICATION DECLARATION BY THE ASSIGNEE	Docket Number 01723512

At least one error upon which reissue is based is described as follows:

Failure to appreciate the full scope of the invention. M.P.E.P. 1402.

One reason, for example, is that "powder" is added to claim 1 to clarify the invention.

(Attach additional sheets, if needed.)

All errors corrected in this reissue application arose without any deceptive intention on the part of the applicant.

I hereby appoint:

[X] Practitioners associated with Customer Number 26565

OR

[ ] Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Correspondence Address: Direct all communications about the application to:

[X] The address associated with Customer Number 26565

OR

[ ] Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this declaration is directed.

Signature	Date 12/19/2007
Full name of person signing (given name, family name) Michael F. Nichols Ph. D.	
Address of Assignee 321 University Hall, Columbia, Missouri 65211	

[Page 2 of 2]

REISSUE APPLICATION: CONSENT OF ASSIGNEE; STATEMENT OF NON-ASSIGNMENT	Docket Number (Optional) 01723512

This is part of the application for a reissue patent based on the original patent identified below.

Name of Patentee(s): The Curators of the University of Missouri

Patent Number	Date Patent Issued
5,840,737	11/24/1998

Title of Invention: Omeprazole Solution and Method for Using Same

1. [X] Filed herein is a statement under 37 CFR 3.73(b) (Form PTO/SB/96)

2. [ ] Ownership of the patent is in the inventor(s), and no assignment of the patent is in effect

One of boxes 1 or 2 above must be checked. If multiple assignees, complete this form for each assignee. If box 2 is checked, skip the next entry and go directly to "Name of Assignee".

The written consent of all assignees and inventors owning an undivided interest in the original patent is included in this application for reissue.

The assignee(s) owning an undivided interest in said original patent is/are The Curators of the University of Missouri and the assignee(s) consents to the accompanying application for reissue.

Name of assignee/inventor (if not assigned): The Curators of the University of Missouri

Signature	Date
[signature]	12/19/2007

Typed or printed name and title of person signing for assignee (if assigned)

Michael F. Nichols Ph. D.
Vice President of Research and Economic Development

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: The Curators of the University of Missouri

Application No./Patent No.: 6,340,737 Filed/Issue Date: November 24, 1998

Entitled: Omeprazole Solution and Method for Using Same

The Curators of the University of Missouri, a (Name of Assignee) a university, public corporation and body politic of the state of Missouri (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is

1. [✓] the assignee of the entire right, title, and interest; or

2. [ ] an assignee of less than the entire right, title and interest.
(The extent (by percentage) of its ownership interest is _____ %)

in the patent application/patent identified above by virtue of either:

A. [✓] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 008114, Frame 0335, or for which a copy thereof is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
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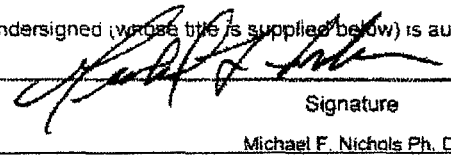
[✓] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.



Signature — Date: 12/19/2007

Michael F. Nichols Ph. D. — 573 884-3553

Printed or Typed Name — Telephone Number

Vice President of Research and Economic Development

Title

Docket No. 01723512

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Phillips, J. O.	ATTORNEY DOCKET:	01723512
PATENT NO.:	5,840,737	GROUP ART UNIT:	1625
FILED:	July 15, 1996	EXAMINER:	Unknown
TITLE:	Omeprazole Solution and Method for Using Same		
DATE:	December 20, 2007	CUSTOMER NO.:	26565

Mail Stop: Reissue
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Dear Sir:

The above referenced patent, enclosed herewith, is filed under 35 U.S.C. § 251 as a reissue of U.S. Patent No. 5,840,737. Prior to examination of this new reissue application, please amend the application as requested herein.

Amendments to the Claims begins on page 2.

Remarks begins on page 5.

Amendments to the Claims:

This listing of claims will replace all prior versions and listing of claims in the application. The following amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed.

Complete Listing of Claims:

What is claimed is:

1. (Currently Amended) A method for treating gastric acid disorders by administering to a patient a single dose of a pharmaceutical composition of omeprazole or lansoprazole powder in a pharmaceutically acceptable carrier consisting essentially of a bicarbonate salt of a Group IA metal wherein said administering step consists of providing to the patient orally a single dose of an aqueous solution or[,] suspension of the pharmaceutical composition without requiring further administration of the bicarbonate salt of the Group IA metal.

2. (Original) A method according to claim 1, wherein the Group IA metal is sodium.

3. (Original) A method according to claim 1, wherein the Group IA metal is potassium.

4. (Currently Amended) A method according to claim 1, wherein the concentration of omeprazole in the composition ranges from approximately 0.5 mg/ml to approximately 6.0 mg/ml.

5. (Currently Amended) A method according to claim 3, wherein the concentration of omeprazole in said composition ranges from approximately 1.0 mg/ml to approximately 4.0 mg/ml.

6. (Original) A method as set forth in claim 5, wherein the concentration of omeprazole in the composition is approximately 2.0 mg/ml.

7. (Original) A method as set forth in claim 1, wherein the concentration of the bicarbonate salt of the Group IA metal in the composition ranges from approximately 5.0% to approximately 60.0%.

8. (Original) A method as set forth in claim 7, wherein the concentration of the bicarbonate salt of the Group IA metal in the composition ranges from approximately 7.5% to approximately 10.0%.

9. (Original) A method as set forth in claim 8, wherein the concentration of the bicarbonate salt of the Group IA metal is approximately 8.4%.

10. (Original) A method as set forth in claim 1, wherein the single dosage form includes a concentration of bicarbonate ranging from approximately 0.75 meq to 1.5 meq per milliliter.

11. (Original) A method as set forth in claim 10, wherein the amount of the bicarbonate in the single dosage form is less than approximately 12 mEq/20 mg dose of omeprazole.

12. (Original) A method as set forth in claim 1, wherein the single dosage form is administered in a volume of between approximately 10 ml and 20 ml.

13. (New) A method for treating gastric acid disorders by administering to a patient a single dose of a pharmaceutical composition of omeprazole in a pharmaceutically acceptable carrier consisting essentially of a bicarbonate salt of a Group IA metal wherein said administering step consists of providing to the patient orally a single dose of an aqueous solution or suspension of the pharmaceutical composition without requiring further administration of the bicarbonate salt of the Group IA metal, wherein the concentration of omeprazole in said composition ranges from approximately 1.0 mg/ml to approximately 4.0 mg/ml.

14. (New) A method for treating gastric acid disorders by administering to a patient a single dose of a pharmaceutical composition of omeprazole in a pharmaceutically acceptable carrier consisting essentially of a bicarbonate salt of a Group IA metal wherein said administering step consists of providing to the patient orally a single dose of an aqueous solution or suspension of the pharmaceutical composition without requiring further administration of the bicarbonate salt of the Group IA metal, wherein the concentration of omeprazole in said composition is approximately 2.0 mg/ml.

15. (New) A method for treating gastric acid disorders by administering to a patient a single dose of a pharmaceutical composition of omeprazole in a pharmaceutically acceptable carrier consisting essentially of a bicarbonate salt of a Group IA metal wherein said administering step consists of providing to the patient orally a single dose of an aqueous solution or suspension of the pharmaceutical composition without requiring further administration of the bicarbonate salt of the Group IA metal, wherein the amount of the bicarbonate in the single dosage form is less than approximately 12 mEq/20 mg dose of omeprazole.

16. (New) A method for treating gastric acid disorders by administering to a patient a single dose of a pharmaceutical composition of omeprazole or lansoprazole in a pharmaceutically acceptable carrier consisting essentially of a bicarbonate salt of a Group IA metal wherein said administering step consists of providing to the patient orally a single dose of an aqueous solution or suspension of the pharmaceutical composition without requiring further administration of the bicarbonate salt of the Group IA metal, wherein the single dosage form is administered in a volume of between approximately 10 ml and approximately 20 ml.

17. (New) The method of claim 1, wherein the pharmaceutical composition comprises omeprazole powder and the bicarbonate salt of a Group IA metal is sodium bicarbonate.

18. (New) The method of claim 17, wherein the pharmaceutical composition further comprises a thickening agent.

19. (New) The method of claim 17, wherein the sodium bicarbonate is present in an amount of about 0.375 to about 0.75 mEq sodium bicarbonate per mg of omeprazole powder.

20. (New) The method of claim 18, wherein the sodium bicarbonate is present in an amount of about 0.375 to about 0.75 mEq sodium bicarbonate per mg of omeprazole powder.

21. (New) The method of claim 19, wherein the omeprazole powder is present in an amount of about 10 mg to about 40 mg.

22. (New) The method of claim 20, wherein the omeprazole powder is present in an amount of about 10 mg to about 40 mg.

23. (New) The method of claim 21, wherein upon oral administration of the suspension at least some of the omeprazole is absorbed within about 10 to about 12 minutes after administration.

24. (New) The method of claim 22, wherein upon oral administration of the suspension at least some of the omeprazole is absorbed within about 10 to about 12 minutes after administration.

Docket No. 01723512

REMARKS

Support for the new claims can be found throughout the specification and claims as originally filed and in the priority documents for this application.

Support for the amendment to claim 1 can be found in the specification as issued at least at column 9, lines 43 to 57.

New claims 13-16 have been written in independent form. Support for new claim 13-16 can be found in the claims as issued at least at original claims 5, 6, 11 and 12 respectively. Support for new claims 17-24 can be found throughout the specification and claims as filed. No new matter has been added.

Conclusion

For at least the foregoing reasons, it is respectfully submitted that claims 1-24 are in condition for allowance. Early and favorable consideration is respectfully requested, and the Examiner is encouraged to contact the undersigned with any questions or to otherwise expedite prosecution. Further, none of Applicant's amendments or cancellations are to be construed as dedicating any such subject matter to the public, and Applicant reserves all rights to pursue any such subject matter in this or a related patent application.

Kindly contact the undersigned with any questions or to otherwise expedite prosecution.

Respectfully submitted,

Joseph A. Mahoney
Registration No. 38,956

CUSTOMER NUMBER 26565
MAYER BROWN LLP
P.O. Box 2828
Chicago, IL 60690-2828
Telephone: (312) 701-8979
Facsimile: (312) 706-9000

US005840737A

United States Patent [19]

Phillips

[11] Patent Number: 5,840,737

[45] Date of Patent: Nov. 24, 1998

[54] **OMEPRAZOLE SOLUTION AND METHOD FOR USING SAME**

[75] Inventor: **Jeffrey Owen Phillips**, Columbia, Mo.

[73] Assignee: **The Curators of the University of Missouri**, Columbia, Mo.

[21] Appl. No.: **680,376**

[22] Filed: **Jul. 15, 1996**

Related U.S. Application Data

[60] Provisional application No. 60/009,608, Apr. 4, 1996.

[51] **Int. Cl.**[6] **A61K 31/44**

[52] **U.S. Cl.** **514/338**

[58] **Field of Search** 514/338

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(List continued on next page.)

Primary Examiner—Jane Fan

Attorney, Agent, or Firm—Kohn & Associates

[57] **ABSTRACT**

A pharmaceutical composition includes an aqueous solution/suspension of omeprazole or other substituted benzimidazoles and derivatives thereof in a pharmaceutically acceptable carrier comprising a bicarbonate salt of a Group IA metal. A method for treating and/or preventing gastrointestinal conditions by administering to a patient a pharmaceutical composition including an aqueous solution/suspension of omeprazole or other substituted benzimidazoles and derivatives thereof in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal wherein the administering step consists of a single dosage form without requiring further administering of the bicarbonate salt of the Group IA metal. A pharmaceutical composition for making a solution/suspension of omeprazole or other substituted benzimidazoles and derivatives thereof includes omeprazole or other substituted benzimidazoles and derivatives thereof and a bicarbonate salt of a Group IA metal in a form for convenient storage whereby when the composition is dissolved in aqueous solution, the resulting solution is suitable for enteral administration.

12 Claims, 1 Drawing Sheet

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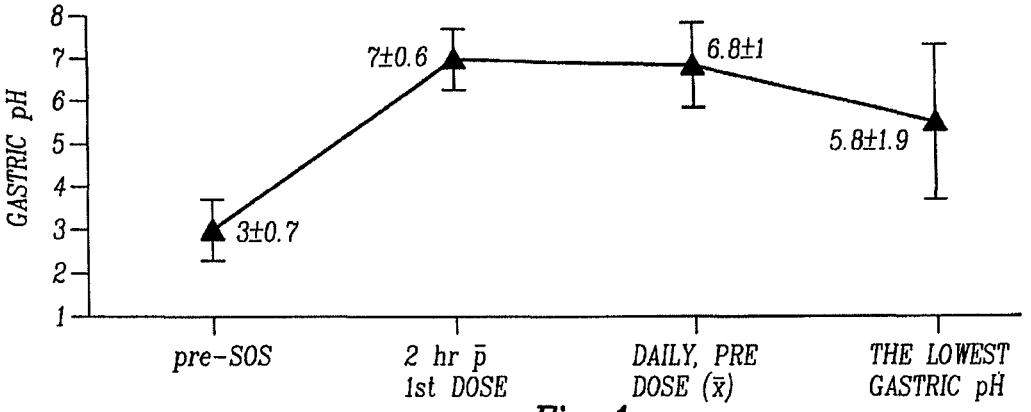
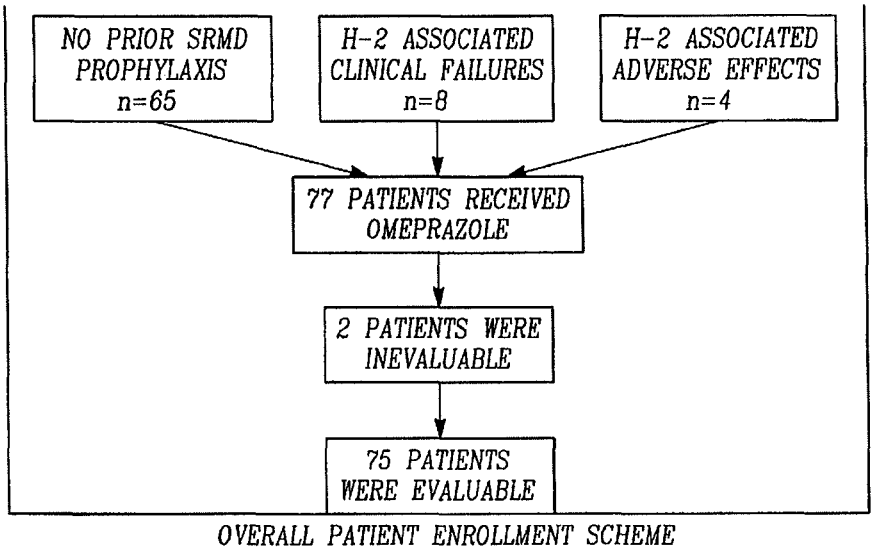


Fig-1



OVERALL PATIENT ENROLLMENT SCHEME

Fig-2

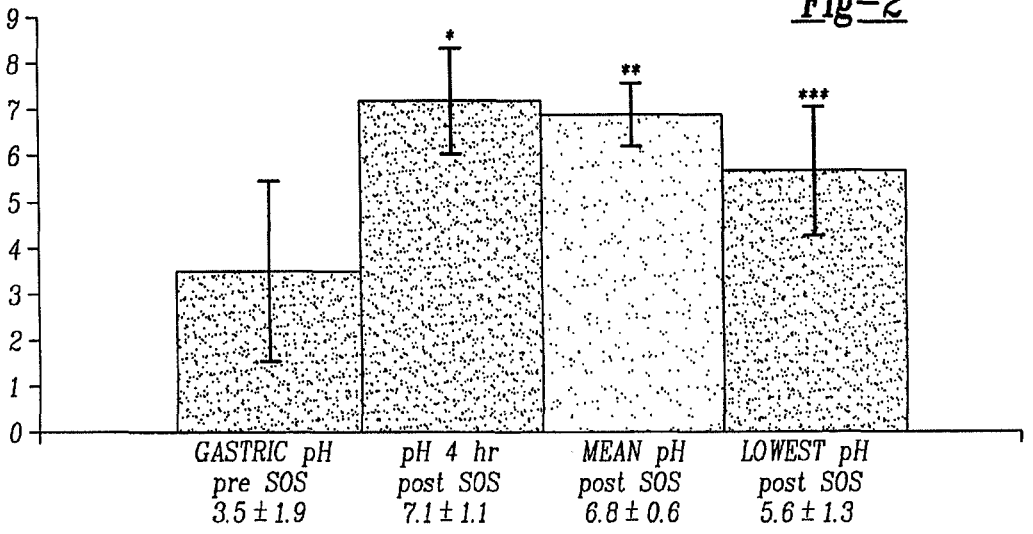


Fig-3

OMEPRAZOLE SOLUTION AND METHOD FOR USING SAME

This application is a continuation-in-part of U.S. Prov. App. Ser. No. 60/009,608 filed on Jan. 4, 1996.

TECHNICAL FIELD

The present invention relates to a pharmaceutical preparation containing a substituted benzimidazole. More particularly, the present invention relates to a substituted benzimidazole solution/suspension suitable for oral administration.

BACKGROUND OF THE INVENTION

Omeprazole is a substituted benzimidazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole, that inhibits gastric acid secretion. Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H_2 histamine antagonist properties. Drugs of this class suppress gastric acid secretion by the specific inhibition of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell.

Typically, omeprazole in the form of a delayed-release capsule, is prescribed for short-term treatment of active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive systematic GERD, and pathological hypersecretory conditions such as Zollinger Ellison syndrome. These conditions are caused by an imbalance between acid and pepsin production, called aggressive factors, and mucous, bicarbonate, and prostaglandin production, called defensive factors.

These above-listed conditions commonly arise in healthy or critically ill patients and may be accompanied by significant upper gastrointestinal bleeding. H_2 antagonists, antacids, and sucralfate are commonly administered to minimize the pain and the complications related to these conditions. These drugs have certain disadvantages associated with their use. Some of these drugs are not completely effective in the treatment of the aforementioned conditions and/or produce adverse side effects, such as mental confusion, constipation, diarrhea, thrombocytopenia, (lowered platelet count) and/or are relatively costly modes of therapy as they require the use of automated infusion pumps for continuous intravenous delivery.

Patients with significant physiologic stress are at risk for stress-related gastric mucosal damage and subsequent upper gastrointestinal bleeding (Marrone and Silen, 1984). Risk factors that have been clearly associated with the development of stress-related mucosal damage are mechanical ventilation, coagulopathy, extensive burns, head injury, and organ transplant (Zinner et al., 1981; Larson et al., 1984; Czaja et al., 1974; Skillman et al., 1969; and Cook et al., 1994). One or more of these factors are often found in critically ill, intensive care unit patients. A recent cohort study challenges other risk factors previously identified such as acid-base disorders, multiple trauma, significant hypertension, major surgery, multiple operative procedures, acute renal failure, sepsis, and coma (Cook et al., 1994). Regardless of the risk type, stress-related mucosal damage results in significant morbidity and mortality. Clinically significant bleeding occurs in at least twenty percent of patients with one or more risk factors who are left untreated (Martin et al., 1993). Of those who bleed, approximately ten percent require surgery (usually gastrectomy) with a

reported mortality of thirty percent to fifty percent (Czaja et al., 1974; Peura and Johnson, 1985). Those who do not need surgery often require multiple transfusions and prolonged hospitalization. Prevention of stress-related upper gastrointestinal bleeding is an important clinical goal.

In addition to general supportive care, the use of drugs to prevent stress-related mucosal damage is considered by many to be the standard of care (AMA Drug Evaluations). However, general consensus is lacking about which drugs to use in this setting (Martin et al., 1993; Gafter et al., 1989; Martin et al., 1992). In two recent meta-analyses (Cook et al., 1991; Tryba, 1994), antacids, sucralfate, and H_2-antagonists were all found to be superior to placebo and similar to one another in preventing upper gastrointestinal bleeding. Yet, prophylactic agents are withdrawn in fifteen to twenty percent of patients in which they are employed because of failure to prevent bleeding, or control pH (Ostro et al., 1985; Siepler, 1986; Ballesteros et al., 1990), or because of adverse effects (Gafter et al., 1989; Sax, 1987; Vial et al., 1991; Cantu and Korek, 1991; Spychal and Wickham, 1985). In addition, the characteristics of an ideal agent for the prophylaxis of stress gastritis and concluded that none of the agents currently in use fulfill their criteria (Smythe and Zarowitz, 1994).

Omeprazole reduces gastric acid production by irreversibly inhibiting the H+/K+ ATPase of the parietal cell—the final common pathway for gastric acid secretion (Fellenius et al., 1981; Wallmark et al., 1985; Frylund et al., 1988). Because this drug maintains gastric pH control throughout the dosing interval and has a very good safety profile, it is a logical choice for stress ulcer prophylaxis. The absence of an intravenous or oral liquid dosage form in the United States, however, has limited the testing and use of omeprazole in the critical care patient population. Subsequently, Barie et al (Barie and Hariri, 1992) described the use of omeprazole enteric-coated pellets administered through a nasogastric tube to control gastrointestinal hemorrhage in a critical care patient with multi-organ failure.

Stress ulcer prophylaxis has become routine therapy in intensive care units in most hospitals (Fabian et al, 1993.; Cook et al., 1991). Controversy remains regarding pharmacologic intervention to prevent stress-related bleeding in critical care patients. It has been suggested that the incidence and risk of gastrointestinal bleeding has decreased in the last ten years and drug therapy may no longer be needed (Cook et al., 1994; Tryba, 1994; Schepp, 1993). This reasoning is not supported by a recent placebo-controlled study. Martin et al. conducted a prospective, randomized, double-blind, placebo-controlled comparison of continuous-infusion cimetidine and placebo for the prophylaxis of stress-related mucosal damage (Marten et al., 1993). The study was terminated early because of excessive bleeding-related mortality in the placebo group. It appears that the natural course of stress-related mucosal damage in a patient at risk who receives no prophylaxis remains significant. In the placebo group, thirty-three percent of patients developed clinically significant bleeding, nine percent required transfusion, and six percent died due to bleeding-related complications. In comparison, fourteen percent of cimetidine-treated patients developed clinically significant bleeding, six percent required transfusions, and 1.5% died due to bleeding-related complication; the difference in bleeding rates between treatment groups was statistically significant. This study clearly demonstrated that continuous-infusion cimetidine reduced morbidity in critical care patients. Although, these data were used to support the approval of continuous-infusion cimetidine by the Food and Drug Administration for stress ulcer

prophylaxis, H_2-antagonists fall short of being the optimal pharmacotherapeutic agents for preventing of stress-related mucosal bleeding.

Another controversy surrounding stress ulcer prophylaxis is which drug to use. In addition to the various H_2-antagonists, antacids and sucralfate are other treatment options for the prophylaxis of stress-related mucosal damage. An ideal drug in this setting should possess the following characteristics: prevent stress ulcers and their complications, be devoid of toxicity, lack drug interactions, be selective, have minimal associated costs (such as personnel time and materials), and be easy to administer (Smythe and Zarowitz, 1994).

Some have suggested that sucralfate is possibly the ideal agent for stress ulcer prophylaxis (Smythe and Zarowitz, 1994). Randomized, controlled studies support the use of sucralfate (Borrero et al., 1986; Tryba, 1987; Cioffi et al., 1994; Driks et al., 1987), but data on critical care patients with head injury, trauma, or burns are limited. In addition, a recent study comparing sucralfate and cimetidine plus antacids for stress ulcer prophylaxis reported clinically significant bleeding in three of forty-eight (6%) sucralfate-treated patients, one of whom required a gastrectomy (Cioffi et al., 1994). In the study performed by Driks and coworkers that compared sucralfate to conventional therapy (H_2-antagonists, antacids, or H_2-antagonists plus antacids), the only patient whose death was attributed to stress-related upper gastrointestinal bleeding was in the sucralfate arm (Driks et al., 1987).

H_2-antagonists fulfill many of the criteria for an ideal stress ulcer prophylaxis drug. Yet, clinically significant bleeds can occur during H_2-antagonist prophylaxis (Martin et al., 1993; Cook et al., 1991; Schuman et al., 1987) and adverse events are not uncommon in the critical care population (Gafter et al., 1989; Sax, 1987, Vial et al., 1991; Cantu and Korek, 1991; Spychal and Wickham, 1985). One reason proposed for the therapeutic H_2-antagonist failures is lack of pH control throughout the treatment period (Ostro et al., 1985). Although the precise pathophysiologic mechanism(s) involved in stress ulceration are not clearly established, the high concentration of hydrogen ions in the mucosa (Fiddian-Green et al., 1987) or gastric fluid in contact with mucosal cells appears to be an important factor. A gastric pH >3.5 has been associated with a lower incidence of stress-related mucosal damage and bleeding (Larson et al., 1984; Skillman et al., 1969; Skillman et al., 1970; Priebe and Skillman, 1981). Several studies have shown that H_2-antagonists, even in maximal doses, do not reliably or continuously increase intragastric pH above commonly targeted levels (3.5 to 4.5). This is true especially when used in fixed-dose bolus regimens (Ostro, 1985; Siepler, 1986; Ballesteros et al., 1990). In addition, gastric pH levels tend to trend downward with time when using a continuous-infusion of H_2-antagonists, which may be the result of tachyphylaxis (Ostro et al., 1985; Wilder-Smith and Merki, 1992).

Because stress ulcer prophylaxis is frequently employed in the intensive care unit, it is essential from both a clinical and economic standpoint to optimize the pharmacotherapeutic approach. In an attempt to identify optimal therapy, cost of care becomes an issue. All treatment costs should be considered, including the costs of treatment failures and drug-related adverse events. While the actual number of failures resulting in mortality is low, morbidity (e.g., bleeding that requires blood transfusion) can be high, even though its association with the failure of a specific drug is often unrecognized.

Omeprazole represents an advantageous alternative to the use of H_2 antagonists, antacids, and sucralfate as a treatment for complications related to stress-related mucosal damage. However, in its current form (capsules containing an enteric-coated granule formulation of omeprazole), omeprazole can be difficult or impossible to administer to patients who are unable (critically ill patients, children, elderly, patients suffering from dysphagia) or patients who are either unwilling or unable to swallow tablets or capsules. Therefore, it would be desirable to formulate an omeprazole solution which can be enterally delivered to a patient thereby providing the benefits of omeprazole without the drawbacks of the current capsule dose form.

Omeprazole has been formulated in many different embodiments such as in a mixture of polyethylene glycols formed a mixture of adeps solidus and sodium lauryl sulfate in a soluble, basic amino acid to yield a formulation designed for administration in the rectum as shown in U.S. Pat. No. 5,219,870 to Kim. U.S. Pat No. 5,395,323 to Berglund ('323) discloses a device for mixing a pharmaceutical from a solid supply into a parenterally acceptable liquid form for parenteral administration to a patient. The '323 patent teaches the use of an omeprazole tablet which is placed in the device and dissolved by normal saline, and infused into the patient. This device and method of infusing omeprazole does not provide the omeprazole solution as an enteral product nor is this omeprazole solution directly administered to the diseased or affected areas, namely the stomach and upper gastrointestinal tract, nor does this omeprazole formulation provide the immediate anti-acid effect of the present formulation.

U.S. Pat. No. 4,786,505 to Lovgren et al., discloses a pharmaceutical preparation containing omeprazole together with an alkaline reacting compound or an alkaline salt of omeprazole optionally together with an alkaline compound as a core material in a tablet formulation. The use of the alkaline material, which can be chosen from such substances as the sodium salt of carbonic acid, are used to form a "micro-pH" around each omeprazole particle to protect the omeprazole which is highly sensitive to acid pH. The powder mixture is then formulated to small beads, pellets, tablets and may be loaded into capsules by conventional pharmaceutical procedures.

This formulation of omeprazole does not provide an omeprazole dose form which can be enterally administered to a patient who may be unable and/or unwilling to swallow capsules or pellets nor does it teach a convenient form which can be used to make an omeprazole solution.

Several buffered omeprazole solutions have been disclosed. Andersson et al., 1993; Landahl et al., 1992; Andersson et al., 1990; Regardh et al., 1990; Andersson et al., 1990; Pilbrant et al., 1985.

All of the buffered omeprazole solutions described in these references were administered orally and were given to healthy subjects who were able to ingest the oral dose. In all of these studies, omeprazole was suspended in a solution including sodium bicarbonate, as a pH buffer, in order to protect the acid sensitive omeprazole during administration.

In all of these studies, repeated administration of sodium bicarbonate both prior to, during, and following omeprazole administration were required in order to prevent acid degradation of the omeprazole given via the oral route of administration. As a result, the ingestion of the large amounts of sodium bicarbonate and large volumes of water were required. In the above-cited studies, as much as 48 mmoles of sodium bicarbonate in 300 ml of water must be ingested for a single dose of omeprazole to be orally administered.

Initial reports of increased frequency of pneumonia in patients receiving stress ulcer prophylaxis with agents that raise gastric pH has influenced the pharmacotherapeutic approach to management of critical care patients. However, several recent studies (Simms et al., 1991; Pickworth et al., 1993; Ryan et al., 1993; Fabian et al., 1993), a meta-analysis (Cook et al., 1991), and a closer examination of the studies that initiated the elevated pH-associated pneumonia hypotheses (Schepp, 1993) cast doubt on a causal relationship. The relationship between pneumonia and antacid therapy is much stronger than for H_2-antagonists. The shared effect of antacids and H_2-antagonists on gastric pH seems an irresistible common cause explanation for nosocomial pneumonia observed during stress ulcer prophylaxis. However, there are important differences between these agents that are not often emphasized (Laggner et al., 1989). When antacids are exclusively used to control pH in the prophylaxis of stress-related upper gastrointestinal bleeding, large volumes are needed. Volume, with or without subsequent reflux, may be the underlying mechanism(s) promoting the development of pneumonia in susceptible patient populations rather than the increased gastric pH. The rate of pneumonia in our study (12%) was not unexpected in this critical care population and compares with sucralfate, which does not significantly raise gastric pH (Pickworth et al., 1993; Ryan et al., 1993).

The buffered omeprazole solutions of the above cited prior art require large amounts of sodium bicarbonate to be given by repeated administration. This is necessary to prevent acid degradation of the omeprazole. The administration of large amounts of sodium bicarbonate can produce at least four significant adverse effects which can dramatically reduce the efficacy of the omeprazole in patients and reduce the overall health of the patients. In the above-cited studies, basically healthy volunteers rather than sick patients were given only one or two dosages of omeprazole utilizing pre-dosing and post-dosing with large volumes of sodium bicarbonate. This dosing protocol would not be suitable for sick or critically ill patients who must receive multiple doses of omeprazole.

Since bicarbonate is usually neutralized in the stomach or is absorbed, such that belching results, patients with gastroesophageal reflux may exacerbate or worsen their gastroesophageal reflux disease as the belching can cause upward movement of stomach acid (Brunton, 1990).

Patients with conditions, such as hypertension or heart failure, are standardly advised to avoid the intake of excessive sodium as this can cause aggravation or exacerbation of their hypertensive conditions (Brunton, 1990).

Additionally, patients with numerous conditions which typically accompany critical illness should avoid the intake of excessive sodium bicarbonate as it can cause metabolic alkalosis which can result in a serious worsening of the patient's condition. Furthermore, excessive antacid intake (such as sodium bicarbonate) can result in drug interactions which produce serious adverse effects. For example, by altering gastric and urinary pH, antacids can alter rates of drug dissolution and absorption, bioavailability, and renal elimination (Brunton, 1990).

Since buffered omeprazole solution requires prolonged administration of the antacid, sodium bicarbonate, it makes it difficult for patients to comply with the above recommendation.

In addition to the disadvantages associated with excessive intake of sodium bicarbonate, the above-cited prior art teaches a relatively complex regimen for the oral administration of omeprazole. For example, in the Pilbrant et al. (1985) reference, the oral omeprazole administration protocol calls for administering to a subject who has been fasting for at least ten hours, a solution of 8 mmoles of sodium bicarbonate in 50 ml of water. Five minutes later, the subject ingests a suspension of 60 mg of omeprazole in 50 ml of water which also contains 8 mmoles of sodium bicarbonate. This is rinsed down with another 50 ml of 8 mmoles sodium bicarbonate solution. Ten minutes after the ingestion of the omeprazole dose, the subject ingests 50 ml of bicarbonate solution (8 mmoles). This is repeated at twenty minutes and thirty minutes post omeprazole dosing to yield a total of 48 mmoles of sodium bicarbonate and 300 ml of water in total which are ingested by the subject for a single omeprazole dose.

Not only does this regimen require the ingestion of excessive amounts of bicarbonate and water, it is unlikely that a healthy patient would comply with this regimen for each dose of omeprazole over the course of a prescribed omeprazole protocol. It is unlikely or even improbable that a critically ill patient would be able to comply with this regimen.

Even in healthy patients, the complexity of the drug regimen leads to the conclusion that patients would be unlikely to comply with this regimen thereby leading to a lack of beneficial outcome for the patient. It is well documented that patients who are required to follow complex schedules for drug administration are non-compliant and, thus, the efficacy of the buffered omeprazole solutions of the prior art would be expected to be reduced due to non-compliance. Compliance has been found to be markedly reduced when patients are required to deviate from a schedule of one or two (usually morning and night) doses of a medication per day. The use of the prior art buffered omeprazole solutions which require administration protocols with numerous steps, different drugs (sodium bicarbonate+omeprazole+PEG400 versus sodium bicarbonate alone), and specific time allotments between each stage of the total omeprazole regimen in order to achieve efficacious results is clearly in contrast with both current drug compliance theories and human nature.

The prior art (Pilbrant et al., 1985) teaches that the buffered omeprazole suspension can be stored at refrigerator temperatures for a week and deep frozen for a year while still maintaining 99% of their initial potency. It would be desirable to have an omeprazole solution which could be stored at room temperature or in a refrigerator for periods of time which exceed those of the prior art while still maintaining 99% of the initial potency. Additionally, it would be advantageous to have a form of the omeprazole and bicarbonate which can be utilized to instantly make the omeprazole solution/suspension of the present invention which is supplied in a solid form which imparts the advantages of improved shelf-life at room temperature, lower cost to produce, less expensive shipping costs, and which is less expensive to store.

It would, therefore, be desirable to have an omeprazole formulation which provides a cost effective means for the treatment of the aforementioned conditions without the adverse effect profile of H_2 receptor antagonist, antacids, and sucralfate. Further, it would be desirable to have an omeprazole formulation which is convenient to prepare and administer to patients unable ingest capsules, which is rapidly absorbed, can be enterally delivered directly to the desired treatment region, which does not clog indwelling tubes, such as nasogastric tubes or other similar tubes, and which acts as an antacid immediately upon delivery. Furthermore, it would be desirable to have a pharmaceutical

composition which is highly efficacious for the treatment of the aforementioned conditions.

The present invention provides a solution/suspension of omeprazole, lansoprazole or other suitable benzimidazoles which is suitable for enteral administration which includes all of the aforementioned advantages.

SUMMARY OF THE INVENTION AND ADVANTAGES

In accordance with the present invention, there is provided a pharmaceutical composition including an aqueous solution/suspension of omeprazole or other substituted benzimidazoles and derivatives thereof in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal.

The present invention further provides a method for treating and/or preventing gastrointestinal conditions by administering to a patient a pharmaceutical composition including an aqueous solution/suspension of omeprazole and derivatives thereof in a pharmaceutically acceptable carrier comprising a bicarbonate salt of a Group IA metal wherein the administration step consists of a single dosage without requiring further administration of the bicarbonate salt of the Group IA metal.

The present invention further provides a pharmaceutical composition for use making a solution/suspension of omeprazole or other substituted benzimidazoles and derivatives thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Other advantages of the present invention will be readily appreciated as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawing wherein:

FIG. **1** is a graph showing the effect of the omeprazole solution/suspension of the present invention on gastric pH in patients at risk for upper gastrointestinal bleeding from stress-related mucosal damage;

FIG. **2** is a flow chart illustrating a patient enrollment scheme; and

FIG. **3** is a bar graph illustrating gastric pH both pre- and post- administration of omeprazole solution/suspension according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

A pharmaceutical composition which can include an aqueous solution/suspension of omeprazole or other substituted benzimidazoles such as lansoprazole, and derivatives thereof in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal is disclosed. For the purposes of description, the composition includes both solutions and/or suspensions of the omeprazole or other substituted benzimidazoles. Hereinafter, the use of the term "solution" includes solutions and/or suspensions of the substituted benzimidazoles.

The pharmaceutical composition of the present invention is prepared by mixing omeprazole (Merck & Co. Inc., West Point, Pa.) or other substituted benzimidazoles and derivatives thereof with a solution including a bicarbonate salt of a Group IA metal. Preferably, omeprazole powder or granules, which can be obtained from a capsule, are mixed with a sodium bicarbonate solution to achieve a desired final omeprazole concentration. The concentration of omeprazole in the solution/suspension can range from approximately 0.5 mg/ml to approximately 6.0 mg/ml. The preferred concentration for the omeprazole in the solution/suspension ranges from approximately 1.0 mg/ml to approximately 4.0 mg/ml with 2 mg/ml being the standard concentration.

The pharmaceutically effective carrier includes the bicarbonate salt of the Group IA metal and can be prepared by mixing the bicarbonate salt of the Group IA metal, preferably sodium bicarbonate, with water. The concentration of the bicarbonate salt of the Group IA metal in the composition generally ranges from approximately 5.0 percent to approximately 60.0 percent. Preferably, the concentration of the bicarbonate salt of the Group IA metal ranges from approximately 7.5 percent to approximately 10.0 percent. In a preferred embodiment of the present invention, sodium bicarbonate is the preferred salt of the Group IA metal and is present in a concentration of approximately 8.4 percent.

In a preferred embodiment of the present invention, enterically-coated omeprazole particles are obtained from delayed release capsules (Astra Merck) additionally omeprazole powder can be used. The coated omeprazole particles are mixed with a sodium bicarbonate ($NaHCO_3$) solution which dissolves the enteric coating and forms an omeprazole solution/suspension in accordance with the present invention. It is important to emphasize that the enteric coated pellets of omeprazole must be allowed to completely breakdown in the suspension vehicle or carrier prior to administration. The omeprazole solution/suspension has significant pharmacokinetic advantages over standard time-release omeprazole capsules including: a decreased drug absorbance time (~10 to 12 minutes) following administration for the omeprazole solution versus (~2–3 hours) following administration for the enteric coated pellets; the $NaHCO_3$ solution protects the omeprazole from acid degradation prior to absorption; the $NaHCO_3$ acts as an antacid while the omeprazole is being absorbed; and the solution/suspension can be administered through an existing indwelling tube without clogging, for example, nasogastric or other feeding tubes (jejunal or duodenal) including small bore needle catheter feeding tubes.

As stated above, suitable derivatives of omeprazole can be substituted for the omeprazole or other suitable substituted benzimidazoles without departing from the spirit of the present invention. These derivatives can include, but are not limited to, lansoprozole.

The pharmaceutical composition including the omeprazole and derivatives thereof in a pharmaceutically acceptable carrier of a bicarbonate salt of Group IA metal can be used for the treatment of gastrointestinal conditions including, but not limited to, active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive systematic GERD, and pathological hypersecretory conditions such as Zollinger Ellison Syndrome. These conditions are caused by imbalances between acid and pepsin production, called aggressive factors, and mucous, bicarbonate, and prostaglandin production, called defensive factors. Treatment of these conditions is accomplished by administering to a patient an effective amount of the pharmaceutical composition according to the present invention.

The omeprazole solution/suspension is administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient, the sight and method of administration, scheduling of administration, and other factors known to medical practitioners. The "effective amount" for purposes herein thus

determine by such considerations as are known in the art. The amount must be effective to achieve improvement, including but not limited to, raising of gastric pH, reduced gastrointestinal bleeding, reduction in the need for blood transfusion, improved survival rate, more rapid recovery, or improvement or elimination of systems and other indicators as are selected as appropriate measures by those skilled in the art.

The dosage range of omeprazole or other substituted benzimidazoles and derivatives thereof can range from approximately 2 mg/day to approximately 100 mg/day. The standard daily dosage is typically 20 mg omeprazole in 10 ml of solution.

In the method of the present invention, the omeprazole solution/suspension can be administered in various ways. It should be noted that the omeprazole solution/suspension can be administered as the compound or as the pharmaceutically acceptable salt and can be administered alone or in combination with pharmaceutically acceptable carriers. The compounds can be administered orally or enterally. The formulations can be made more palatable by adding flavorings such as chocolate, root beer, and others.

Additionally, various additives including ambicin which enhance the stability, sterility, and isotonicity of the compositions. Additionally, antimicrobial preservatives, antioxidants, chelating agents, and buffers can be added. However, microbiological evidence shows that this formulation inherently possesses anti-microbial activity. Prevention of the action of microorganisms can be enhanced by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like.

In many cases, it would be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Additionally, thickening agents, such as methyl cellulose, in order to reduce settling the omeprazole or derivatives thereof from the suspension.

The formulations of the present invention can be manufactured in a concentrated form, such as an effervescent tablet, so that upon reaction with water, the aqueous form of the present invention would be produced for oral or enteral administration.

Additionally, the present invention can be manufactured by utilizing micronized omeprazole in place of the omeprazole granules or omeprazole powder in place of omeprazole granules. This process is known as micronization and is utilized in order to produce a particle having a greater diameter. Micronization is the process by which solid drug particles are reduced in size. Since the dissolution rate is directly proportional to the surface area of the solid, and reducing the particle size increases the surface area, reducing the particle size increases the dissolution rate.

Although micronization results in increased surface area causing particle aggregation, which can negate the benefit of micronization and is an expensive manufacturing step, it does have the significant benefit of increasing the dissolution rate of relatively water insoluble drugs, such as omeprazole.

A pharmacological formulation of the omeprazole solution/suspension utilized in the present invention can be administered orally to the patient. A pharmacological formulation of the omeprazole solution/suspension utilized in the present invention is preferably administered enterally. This can be accomplished, for example, by administering the solution/suspension via a nasogastric tube or other indwelling tubes. In order to avoid the critical disadvantages associated with administering large amounts of sodium bicarbonate, the omeprazole solution of the present invention is administered in a single dose which does not require any further administration of bicarbonate following the administration of the omeprazole solution. That is, unlike the prior art omeprazole solutions and administration protocols outlined above, the formulation of the present invention is given in a single dose which does not require administration of bicarbonate either before administration of the omeprazole or after administration of the omeprazole. The present invention eliminates the need to pre- or post-dose with additional volumes of water and sodium bicarbonate. The amount of bicarbonate administered via the single dose administration of the present invention is less than the amount of bicarbonate administered as taught in the prior art references cited above.

The amount of sodium bicarbonate used in the solution/suspension of the present invention is approximately 1 meq (or mmole) sodium bicarbonate per 2 mg omeprazole, with a range of approximately 0.75 meq (mmole) to 1.5 meq (mmole) per 2 mg of omeprazole.

The present invention further includes a pharmaceutical composition for making a solution/suspension of omeprazole or other substituted benzimidazoles and derivatives thereof, which consists essentially of omeprazole or other substituted benzimidazoles and derivatives thereof and a bicarbonate salt of a Group IA metal in a form convenient for storage, whereby when the composition is placed into a aqueous solution, the composition dissolves yielding a solution/suspension suitable for enteral administration to a subject. The pharmaceutical composition is in a solid form prior to dissolution in the aqueous solution. The omeprazole or other substituted benzimidazoles and derivatives thereof and bicarbonate can be formed into a tablet, capsules, or granules, by methods well known to those skilled in the art.

The pharmaceutical composition suitable for making a solution/suspension according to the present invention can further include an effervescing agent to aid in the dissolution of the pharmaceutical composition in the aqueous solution. In the present invention the effervescing agent is sodium bicarbonate.

The resultant omeprazole solution is stable at room temperature for several weeks and inhibits the growth of bacteria or fungi as shown in Example IV below. By providing a pharmaceutical composition including the omeprazole or other substituted benzimidazole and derivatives thereof with bicarbonate in a solid form, which is dissolved in a prescribed amount of aqueous solution to yield the desired concentration of omeprazole and bicarbonate, the cost of production, shipping, and storage are greatly reduced as no liquids are shipped (reducing weight and cost) and there is no need to refrigerate the solid form of the composition or the solution. The resultant solution, can be formulated and then used to provide dosages for a single patient over a course of time or for several patients.

The following experimental data illustrate the utility of the pharmaceutical composition of the present invention.

METHODS

EXAMPLE I

Patients were evaluable if they met the following criteria: had two or more risk factors for SRMD (mechanical ventilation, head injury, severe burn, sepsis, multiple trauma, adult respiratory distress syndrome, major surgery, acute renal failure, multiple operative procedures, coagulatherapy, significant hypotension, acid-base disorder, and hepatic failure), gastric pH of ≦4 prior to study entry, and no concomitant prophylaxis for SRMD.

Nasogastric (ng) tubes were placed in the patients and an omeprazole dosage protocol of 40 mg omeprazole solution/suspension followed by 40 mg omeprazole solution/suspension in eight hours, then 20 mg omeprazole solution/suspension per day, for five days. After each omeprazole solution/suspension administration, nasogastric suction was turned off for thirty minutes.

Results

Eleven patients were evaluable. All patients were mechanically ventilated. Two hours after the initial dose of omeprazole solution/suspension 40 mg omeprazole, all patients had an increase in gastric pH to greater than eight as shown in FIG. 1. Ten of the eleven patients maintained a gastric pH of greater than or equal to four on 20 mg omeprazole solution/suspension. One patient required 40 mg omeprazole solution/suspension per day (closed head injury, five total risk factors for SRMD). Two patients were changed to omeprazole solution/suspension after having developed clinically significant upper gastrointestinal bleeding while receiving conventional intravenous H_2 antagonists. Bleeding subsided in both cases after twenty-four hours. Clinically significant upper gastrointestinal bleeding did not occur in the other nine patients. Overall mortality was 27%, mortality attributable to upper gastrointestinal bleeding was 0%. Pneumonia developed in one patient after initiating omeprazole therapy and was present upon the initiation of omeprazole therapy in another patient. The mean length of prophylaxis was five days.

A pharmacoeconomic analysis revealed a difference in the total cost of care for the prophylaxis of SRMD:

- ranitidine (Zantac®) continuous infusion intravenously (150 mg/24 hours)×five days $125.50;
- cimetidine (Tagamet®) continuous infusion intravenously (900 mg/24 hours)×five days $109.61;
- sucralfate one gm slurry four times a day per (ng) tube× five days $73.00; and
- SOS regimen per (ng) tube×five days $65.70.

Conclusion

This example illustrates the efficacy of the simplified omeprazole solution of the present invention based on the increase in gastric pH, safety and cost/convenience of the omeprazole solution/suspension as a method for SRMD prophylaxis.

EXAMPLE II

Experiments were carried out in order to determine the effect of the omeprazole solution/suspension (omeprazole/sodium bicarbonate solution) administration on the accuracy on subsequent pH measurements through a nasogastric tube.

Methods

The omeprazole solution/suspension was prepared by mixing 10 ml of 8.4% sodium bicarbonate with the contents of a 20 mg capsule of omeprazole (Merck & Co. Inc., West Point, Pa.) to yield a solution/suspension having a final omeprazole concentration of 2 mg/ml. After mixing the omeprazole solution/suspension, it was administered into the stomach, usually, through a nasogastric (ng) tube. Nasogastric tubes from nine different institutions were gathered for an evaluation 400 mg omeprazole solution/suspension was prepared as described above. Artificial gastric fluid (gf) was prepared according to the USP. pH recordings were made in triplicate using a Microcomputer Portable pH meter model 6007 (Jenco Electronics Ltd., Taipai, Taiwan). [1] First the terminal portion (tp) of the nasogastric tubes was placed into a glass beaker containing the gastric fluid. A 5 ml aliquot of gastric fluid was aspirated through each tube and the pH recorded, this was called the "pre-omeprazole solution/suspension measurement". [2] Secondly, the terminal portion (tp) of each of the nasogastric tubes was removed from the beaker of gastric fluid and placed into an empty beaker. Twenty (20) mg of omeprazole solution/suspension was delivered through each of the nasogastric tubes and flushed with 10 ml of tap water. The terminal portion (tp) of each of the nasogastric tubes was placed back into the gastric fluid. After a one hour incubation, a 5 ml aliquot of gastric fluid was aspirated through each nasogastric tube and the pH recorded, this was called the "after 1st dose SOS measurement". [3] After an additional hour had passed, the second step was repeated, this was called the "after 2nd ND dose SOS measurement". In addition to the pre-SOS measurement, the pH of the gastric fluid was checked in triplicate after steps [2] and [3]. A change in the pH measurements of ±0.3 units was considered significant. The Friedman test was used to compare the results. The Friedman test is a two way analysis of variance which is used when more than two related samples are of interest, as in repeated measurements.

Results

The results of this experiments are outlined in Table 1. Table 1 illustrates the results of the pH measurements that were taken during the course of the experiment. These results illustrate that there were no statistically significantly latent effects of omeprazole solution/suspension administration (per nasogastric tube) on the accuracy of subsequent pH measurements obtained through the same nasogastric tube.

EXAMPLE III

Experiments were performed in order to determine the efficacy, safety, and cost of simplified omeprazole suspension in mechanically ventilated critically ill patients who have at least one additional risk factor for stress-related mucosal damage.

Methods

Patients

Seventy-five adult, mechanically ventilated patients with at least one additional risk factor for stress-related mucosal damage. Interventions: Patients received 20 ml omeprazole suspension (containing 40 mg of omeprazole) initially, followed by a second 20 ml dose six-eight hours later, then 10 ml (20 mg) daily. Omeprazole solution/suspension according to the present invention was administered through a nasogastric tube, followed by 5–10 ml of tap water. The nasogastric tube was clamped for one-two hours after each administration.

Measurements and Main Results

The primary outcome measure was clinically significant gastrointestinal bleeding determined by endoscopic evaluation, nasogastric aspirate examination, or heme-positive coffee ground material that did not clear with lavage and was associated with a five percent decrease in hematocrit. Secondary efficacy measures were gastric pH measured four hours after omeprazole was first administered, mean gastric pH after omeprazole was started, and the lowest gastric pH during omeprazole therapy. Safety-related outcomes included the incidence of adverse events and the incidence of pneumonia. No patient experienced clinically significant upper gastrointestinal bleeding after receiving omeprazole suspension. The four-hour post omeprazole gastric pH was 7.1 (mean), the mean gastric pH after starting omeprazole was 6.8 (mean) and the lowest pH after starting omeprazole was 5.6 (mean). The incidence of pneumonia was twelve percent. No patient in this high-risk population experienced an adverse event or a drug interaction that was attributable to omeprazole.

Conclusions

Omeprazole suspension prevented clinically significant upper gastrointestinal bleeding and maintained gastric pH above 5.5 in mechanically ventilated critical care patients without producing toxicity.

Materials and Methods

The study protocol was approved by the Institutional Review Board for the University of Missouri at Columbia.

Study Population

All adult (>18 years old) patients admitted to the surgical intensive care and burn unit at the University of Missouri Hospital with an intact stomach, a nasogastric tube in place, and an anticipated intensive care unit stay of at least forty-eight hours were considered for inclusion in the study. To be included patients also had to have a gastric pH of <4, had to be mechanically ventilated and have one of the following additional risk factors for a minimum of twenty-four hours after initiation of omeprazole suspension: head injury with altered level of consciousness, extensive burns (>20% Body Surface Area), acute renal failure, acid-base disorder, multiple trauma, coagulopathy, multiple operative procedures, coma, hypotension for longer than one hour or sepsis (see Table 2). Sepsis was defined as the presence of invasive pathogenic organisms or their toxins in blood or tissues resulting in a systematic response that included two or more of the following: temperature greater than 38° C. or less than 36° C., heat rate greater than 90 beats/minute, respiratory rate greater than 20 breaths/minute (or $_pO_2$ less than 75 mm Hg), and white blood cell count greater than 12,000 or less than 4000 cells/mm^3 or more than 10 percent bands (Bone, 1991). Patients in whom H_2-antagonist therapy had failed or who experienced an adverse event while receiving H_2-antagonist therapy were also included.

Patients were excluded from the study if they were receiving azole antifungal agents through the nasogastric tube; were likely to swallow blood (e.g., facial and/or sinus fractures, oral lacerations); had severe thrombocytopenia (platelet count less than 30,000 cells/mm ^{3}); were receiving enteral feedings through the nasogastric tube; or had a history of vagotomy, pyloroplasty, or gastroplasty. In addition, patients with a gastric pH above four for forty-eight hours after ICU admission (without prophylaxis) were not eligible for participation. Patients who developed bleeding within the digestive tract that was not stress-related mucosal damage (e.g., endoscopically verified variceal bleeding or Mallory-Weiss tears, oral lesions, nasal tears due to placement of the nasogastric tube) were excluded from the efficacy evaluation and categorized as having non-stress-related mucosal bleeding. The reason for this exclusion is the confounding effect of non-stress-related mucosal bleeding on efficacy-related outcomes, such as the use of nasogastric aspirate inspection to define clinically significant upper gastrointestinal bleeding.

Study Drug Administration

Omeprazole solution/suspension was prepared immediately before administration by the patient's nurse using the following instructions: 1) Empty the contents of one or two 20 mg omeprazole capsule(s) into an empty 10 ml syringe (with 20 gauge needle in place) from which the plunger has been removed. (Omeprazole delayed-release capsules, Merck & Co., Inc., West Point, Pa.). 2) Replace the plunger and uncap the needle. 3) Withdraw 10 ml of 8.4% sodium bicarbonate solution or 20 ml if 40 mg given (Abbott Laboratories, North Chicago, Ill.). The resultant preparation should contain 2 mg omeprazole per ml of 8.4% sodium bicarbonate. 4) Allow the enteric coated pellets of omeprazole to completely breakdown, ~30 minutes (agitation is helpful). The omeprazole in the resultant preparation is partially dissolved and partially suspended. The preparation should have a milky white appearance with fine sediment and should be shaken before using. The solution/suspension was not administered with acidic substances. A high pressure liquid chromatography study was performed that has demonstrated that this preparation of simplified omeprazole suspension maintains >90% potency for seven days at room temperature. This preparation remained free of bacterial and fungal contamination for thirty days when stored at room temperature (see Table 5).

The initial dose of omeprazole solution/suspension was 40 mg, followed by a second 40 mg dose 6–8 hours later, then a 20 mg daily dose administered at 8:00 AM. Each dose was administered through the nasogastric tube. The nasogastric tube was then flushed with 5–10 ml of tap water and clamped for at least one hour. Omeprazole therapy was continued until there was no longer a need for stress ulcer prophylaxis (usually after the nasogastric tube removed and the patient was taking water/food by mouth, or after the patient was removed from mechanical ventilation).

Primary Outcome Measures

The primary outcome measure in this study was the rate of clinically significant stress-related mucosal bleeding defined as endoscopic evidence of stress-related mucosal bleeding or bright red blood per nasogastric tube that did not clear after a 5-minute lavage or persistent Gastroccult (SmithKline Diagnostics, Sunnyville, Calif.) positive coffee ground material for four consecutive hours that did not clear with lavage (at least 100 ml) and produced a 5% decrease in hematocrit.

Secondary Outcome Measures

The secondary efficacy measures were gastric pH measured four hours after omeprazole was administered, mean gastric pH after starting omeprazole and lowest gastric pH during omeprazole administration. Gastric pH was measured immediately after aspirating gastric contents through the nasogastric tube. pH paper (pHydrion improved pH papers, Microessential Laboratory, Brooklyn, N.Y.) was used to measure gastric aspirate pH. The pH range of the test strips was 1 to 11, in increments of one pH unit. Gastric pH was measured before the initiation of omeprazole solution/suspension therapy, immediately before each dose, and every four hours between doses.

Other secondary outcome measures were incidence of adverse events (including drug interactions) and pneumonia. Any adverse event that developed during the study was recorded. Pneumonia was defined using indicators adapted from the Centers for Disease Prevention and Control definition of nosocomial pneumonia (Garner et al., 1988). According to these criteria, a patient who has pneumonia is one who has rales or dullness to percussion on physical examination of the chest or has a chest radiograph that shows new or progressive infiltrate(s), consolidation, cavitation, or pleural effusion and has at least two of the following present: new purulent sputum or changes in character of the sputum, an organism isolated from blood culture, fever or leukocytosis, or evidence of infection from a protective specimen brush or bronchoalveolar lavage. Patients who met the criteria for pneumonia and were receiving antimicrobial agents for the treatment of pneumonia were included in the pneumonia incidence figure. These criteria were also used as an initial screen before the first dose of study drug was administered to determine if pneumonia was present prior to the start of omeprazole suspension.

Cost of Care Analysis

A pharmacoeconomic evaluation of stress ulcer prophylaxis using omeprazole solution/suspension was performed. The evaluation included total drug cost (acquisition and administration), actual costs associated with adverse events (e.g., psychiatry consultation for mental confusion), costs associated with clinically significant upper gastrointestinal bleeding. Total drug cost was calculated by adding the average institutional costs of omeprazole 20 mg capsules, 50 ml sodium bicarbonate vials, and 10 ml syringes with needle; nursing time (drug administration, pH monitoring); pharmacy time (drug preparation); and disposal costs. Costs associated with clinically significant upper gastrointestinal bleeding included endoscopy charges and accompanying consultation fees, procedures required to stop the bleeding (e.g., surgery, hemostatic agents, endoscopic procedures), increased hospital length of stay (as assessed by the attending physician), and cost of drugs used to treat the gastrointestinal bleeding.

Statistical Analysis

The paired t-test (two-tailed) was used to compare gastric pH before and after omeprazole solution/suspension administration and to compare gastric pH before omeprazole solution/suspension administration with the mean and lowest gastric pH value measured after beginning omeprazole.

Results

Seventy-seven patients met the inclusion and exclusion criteria and received omeprazole solution/suspension (see FIG. 2). Two patients were excluded from the efficacy evaluation because the protocol for omeprazole administration was not followed. In one case, the omeprazole enteric-coated pellets had not completely broken down prior to the administration of the first two doses, which produced an erratic effect on gastric pH. The gastric pH increased to above six as soon as the patient was given a dose of omeprazole solution/suspension (in which the enteric coated pellets of omeprazole had been allowed to completely breakdown).

The reason for the second exclusion was that nasogastric suctioning was not turned off after the omeprazole dose was administered. This resulted in a transient effect on gastric pH. The suction was turned off with subsequent omeprazole doses, and control of gastric pH was achieved. Two patients were considered efficacy failures because omeprazole failed to maintain adequate gastric pH control on the standard omeprazole 20 mg/day maintenance dose. When the omeprazole dose 20 was increased to 40 mg/day (40 mg once/day or 20 mg twice/day), gastric pH was maintained above four in both patients. These two patients were included in the safety and efficacy evaluations, including the gastric pH analysis. After the two patients were declared failures, their pH values were no longer followed.

The ages of the remaining seventy-five patients ranged from eighteen to eighty-seven years; forty-two patients were male and thirty-three were female. All patients were mechanically ventilated during the study. Table 2 shows the frequency of risk factors for stress-related bleeding that were exhibited by the patients in this study. The most common risk factors in this population were mechanical ventilation and major surgery. The range of risk factors for any given patient was two to ten, with a mean of 3 (±1) (standard deviation). Five patients enrolled in the study had developed clinically significant bleeding while receiving continuous infusions of ranitidine (150 mg/24 hr) or cimetidine (900 mg/24 hr). In all five cases, the bleeding subsided and the gastric pH rose to above five within thirty-six hours after initiating omeprazole therapy. Three patients were enrolled after having developed two consecutive gastric pH values below three while receiving an H_2-antagonist (in the doses outlined above). In all three cases, gastric pH rose to above five within four hours after omeprazole therapy was initiated. Four other patients were enrolled in this study after experiencing confusion (n=2) or thrombocytopenia (n=2) during H_2-antigens therapy. Within thirty-six hours of switching therapy, these adverse events resolved.

Stress-related Mucosal Bleeding and Mortality

None of the sixty-five patients who received simplified omeprazole suspension as their initial prophylaxis against stress-related mucosal bleeding developed overt or clinically significant upper gastrointestinal bleeding. In four of the five patients who had developed upper gastrointestinal bleeding before study entry, bleeding diminished to the presence of occult blood only (Gastroccult-positive) within eighteen hours of starting omeprazole suspension; bleeding stopped in all patients within thirty-six hours. The overall mortality rate in this group of critically ill patients was eleven percent. No death was attributable to upper gastrointestinal bleeding or the use of omeprazole solution/suspension.

Gastric pH

The mean (±standard deviation) pre-omeprazole gastric pH was 3.5±1.9. Within four hours of omeprazole administration, the gastric pH rose to 7.1±1.1 (se FIG. 3); this difference was significant ($p<0.001$). The differences between pre-omeprazole gastric pH and the mean and lowest gastric pH measurements during omeprazole administration (6.8±0.6 and 5.6±1.3, respectively) were also statistically significant ($p<0.001$).

Safety

Omeprazole solution/suspension was well tolerated in this group of critically ill patients. Only one patient with sepsis experienced an adverse event that may have been drug-related thrombocytopenia. However, the platelet count continued to fall after omeprazole was stopped. The platelet count then returned to normal despite reinstitution of omeprazole therapy. Of note, one patient on a jet ventilator continuously expelled all liquids placed in her stomach up and out through her mouth, and thus was unable to continue on omeprazole. No clinically significant drug interactions with omeprazole were noted during the study period. As stated above, metabolic alkalosis is a potential concern in patients receiving sodium bicarbonate. However, the amount of sodium bicarbonate in omeprazole solution/suspension was small (~12 mEq/10 ml) and no electrolyte abnormalities were found.

Pneumonia

Pneumonia developed in nine (12%) patients receiving omeprazole solution/suspension. Pneumonia was present in an additional five patients before the start of omeprazole therapy.

Pharmacoeconomic evaluation

The average length of treatment was nine days. The cost of care data are listed in Tables 3 and 4. The costs of drug acquisition, preparation, and delivery for some of the traditional agents used in the prophylaxis of stress-related upper gastrointestinal bleeding are listed in Table 3. There were no costs to add from toxicity associated with omeprazole solution/suspension. Since two of seventy-five patients required 40 mg of omeprazole solution/suspension daily to adequately control gastric pH, the acquisition/preparation cost should reflect this. The additional 20 mg of omeprazole with vehicle adds seven cents per day to the cost of care. Therefore, the daily cost of care for omeprazole solution/suspension in the prophylaxis of stress-related mucosal bleeding was $12.60 see Table 4.

Omeprazole solution/suspension is a safe and effective therapy for the prevention of clinically significant stress-related mucosal bleeding in critical care patients. The contribution of many risk factors to stress-related mucosal damage has been challenged recently (6). All of the patients in this study had at least one risk factor that has clearly been associated with stress-related mucosal damage—mechanical ventilation. Previous trials and data from a recently published study show that stress ulcer prophylaxis is of proven benefit in patients at risk and, therefore, it was thought to be unethical to include a placebo group in this study. No clinically significant upper gastrointestinal bleeding occurred during omeprazole solution/suspension therapy. Gastric pH was maintained above 4 on omeprazole 20 mg/day in seventy-three of seventy-five patients. No adverse events or drug interaction associated with omeprazole were encountered.

EXAMPLE IV

The anti-microbial or bacteriostatic effects of the omeprazole solution/suspension were analyzed by applicants.

TABLE I

	ng1	ng2	ng3	ng4	ng5	ng6	ng7	ng8	ng9
[1] gf	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Pre SOS									
[2] gf p	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
1st dose									
1.3←check of fg pH									
[3] gf p	1.3	1.3	1.4	1.4	1.4	1.3	1.4	1.3	1.3
2nd dose									
1.3←check of gf pH							SOS pH = 9.0		

TABLE 2

Mech Vent	Major Surgery	Multi-trauma	Head Injury	Hypo-tension	Renal Failure	Sepsis	Multiple Operation	Acid/ Base	Coma	Liver Failure	Burn
75	61	35	16	14	14	14	12	10	4	2	2

Risk factors present in patients in this study (n = 75)

An omeprazole solution/suspension made according to the present invention was stored at room temperature for four weeks and then was analyzed for fungal and bacterial growth.

Results

Following four weeks of storage at room temperature, no bacterial or fungal growth was detected.

An omeprazole solution/suspension made in accordance with the present invention was stored at room temperature for twelve weeks and then was analyzed for fungal and bacterial growth.

Results

After twelve weeks of incubation at room temperature, no fungal or bacterial growth was detected.

The results of these experiments illustrate the stability and bacteriostatic characteristics of the omeprazole solution/suspension of the present invention.

Throughout this application various publications and patents are referenced by citation and number. Full citations for the publication are listed below. The disclosure of these publications and patents in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

The invention has been described in an illustrative manner, and it is to be understood the terminology used is intended to be in the nature of description rather than of limitation.

Obviously, many modifications and variations of the present invention are possible in light of the above teachings. Therefore, it is to be understood that within the scope of the appended claims, reference numerals are merely for convenience and are not to be in any way limiting, the invention may be practiced otherwise than as specifically described.

TABLE 3

		Per day
RANITIDINE (day 1–9)		
Ranitidine	150 mg/24 hr	6.15
Ancillary Product (1)	Piggyback (60%)	0.75
Ancillary Product (2)	micro tubing (etc.)	2.00
Ancillary Product (3)	filter	.40
Sterile Prep required	yes	
R.N. time ($24/hr)	20 minutes/day (includes pH monitoring)	8.00
R.Ph. time, hood maint.	3 minutes ($40/hr)	2.00
Pump cost	$29/24 hrs × 50%	14.50
TOTAL for 9 days	→	304.20
RAINITIDINE Cost per day	→	33.80
CIMETIDINE (day 1–9)		
Cimetidine	900 mg/24 hr	3.96
Ancillary Product (1)	Piggyback	1.25
Ancillary Product (2)	micro tubing (etc.)	2.00
Ancillary Product (3)	filter	.40
Sterile Prep required	yes	
R.N. time ($24/hr)	20 minutes/day (includes pH monitoring)	8.00
R.Ph. time, hood maint.	3 minutes ($40/hr)	2.00
Pump cost	$29/24 hrs × 50%	14.50
TOTAL for 9 days	→	288.99
CIMETIDINE Cost per day	→	32.11
SUCRALFATE (day 1–9)		
Sucralfate	1 Gm × 4	2.40
Ancillary Product (1)	syringe	.20
Sterile Prep required	no	
R.N. time ($24/hr)	30 minutes/day (includes pH monitoring)	12.00
TOTAL for 9 days	→	131.40

TABLE 3-continued

	Per day
SUCRALFATE Cost per day →	14.60

Note:
Does not include the cost of failure and/or adverse effect.
Acquisition, preparation and delivery costs of traditional agents.

TABLE 4

The average length of treatment was 9 days. Cost of care was calculated from these data:

		Per day	Total
OMEPRAZOLE (day 1)			
Product acquisition cost	40 mg load × 2 (5.66/dose)	11.32	11.32
Ancillary product	materials for solution preparation	0.41	0.41
Ancillary product	syringe w/needle	0.20	0.40
Sterile preparation required	no		
SOS preparation time (R.N.)	6 minutes	2.40	4.80
R.N. time ($24/hr)	21 minutes/day (includes pH monitoring)	8.40	8.40
OMEPRAZOLE (days 2–9)			
Product acquisition cost	20 mg per day	2.83	22.65
Ancillary product	materials for solution preparation	0.41	0.82
Ancillary product	syringe w/needle	0.20	1.60
Sterile preparation required	no		
SOS preparation time (R.N.)	6 minutes	2.40	4.80
R.N. time ($24/hr)	18 minutes/day (includes pH monitoring)	8.40	57.60
2/75 patient require 40 mg simplified omeprazole solution per day (days 2–9)			0.63
No additional cost for adverse effects or for failure			
TOTAL →			113.43
Simplified Omerprazole Solution Cost per day →			12.60

Pharmacoeconomic evaluation of omeprazole cost of care

TABLE 5

Time	Control	1 hour	24 hour	2 day	7 day	14 day
Conc(mg/ml)	2.01	2.07	1.94	1.96	1.97	1.98

Stability of Simplified Omeprazole Solution at room temperature (25° C.)
Values are the mean of three samples

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We claim:

1. A method for treating gastric acid disorders by administering to a patient a single dose of a pharmaceutical composition of omeprazole or lansoprazole in a pharmaceutically acceptable carrier consisting essentially of a bicarbonate salt of a Group IA metal wherein said administering step consists of providing to the patient orally a single dose of an aqueous solution or, suspension of the pharmaceutical composition without requiring further administration of the bicarbonate salt of the Group IA metal.

2. A method according to claim **1,** wherein the Group IA metal is sodium.

3. A method according to claim **1,** wherein the Group IA metal is potassium.

4. A method according to claim **1,** wherein the concentration of omeprazole in the composition range from approximately 0.5 mg/ml to approximately 6.0 mg/ml.

5. A method according to claim **3,** wherein the concentration of omeprazole in said composition range from approximately 1.0 mg/ml to approximately 4.0 mg/ml.

6. A method as set forth in claim **5,** wherein the concentration of omeprazole in the composition is approximately 2.0 mg/ml.

7. A method as set forth in claim **1,** wherein the concentration of the bicarbonate salt of the Group IA metal in the composition ranges from approximately 5.0% to approximately 60.0%.

8. A method as set forth in claim **7,** wherein the concentration of the bicarbonate salt of the Group IA metal in the

composition ranges from approximately 7.5% to approximately 10.0%.

9. A method as set forth in claim **8**, wherein the concentration of the bicarbonate salt of the Group IA metal is approximately 8.4%.

10. A method as set forth in claim **1**, wherein the single dosage form includes a concentration of bicarbonate ranging from approximately 0.75 meq to 1.5 meq per milliliter.

11. A method as set forth in claim **10**, wherein the amount of the bicarbonate in the single dosage form is less than approximately 12 mEq/20 mg dose of omeprazole.

12. A method as set forth in claim **1**, wherein the single dosage form is administered in a volume of between approximately 10 ml and 20 ml.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,840,737
DATED : November 24, 1998
INVENTOR(S) : Jeffrey Owen Phillips

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

On the title page,
first column, Item [60], "April 4,1996"
should read -- Jan. 4,1996--.

Signed and Sealed this

Twenty-fifth Day of May, 1999

Attest:

Attesting Officer

Q. TODD DICKINSON

Acting Commissioner of Patents and Trademarks